Precision medicine in type 2 diabetes

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I certify that all material in this thesis which is not my own work has been identified and that any material that has previously been submitted and approved for the award of a degree by this or any other University has been acknowledged.

(Signature) ……  ……

Abstract

Type 2 diabetes is a progressive disease characterised by raised blood glucose levels. Lowering of blood glucose is required to prevent symptoms of diabetes and to reduce the risk of people with type 2 diabetes developing diabetes-related complications.

Metformin is the initial drug of choice to lower blood glucose for most people. However, for many people metformin eventually fails to control blood glucose and additional medication is required. At least four different types of glucose-lowering medication are recommended after metformin in current type 2 diabetes treatment guidelines. Choosing the best medication is left to the clinician and patient and is a major clinical dilemma.

The degree of glucose-lowering appears to vary greatly between people for all the medication options. The same medication may appear to have a marked effect in one patient but little effect in another. Similarly, only some people develop side-effects. Despite this apparent variation it is largely unknown whether differences in treatment response and risk of side-effects can be predicted based on an individual patient's characteristics.

The aim of this thesis is to establish whether simple patient characteristics are associated with differences in treatment effect for common glucose-lowering medications. If they are, this could inform a precision medicine approach in type 2 diabetes, where medications are targeted to those people most likely to benefit.

In Chapter 1 we review current type 2 diabetes treatment, the opportunity for precision medicine, and methodological challenges in studying precision medicine in type 2 diabetes.

In Chapter 2 we describe the marked changes in prescribing patterns of glucose-lowering therapy in the United Kingdom in recent years, and demonstrate there have been relatively modest changes in important short-term patient outcomes including HbA_{1c} reduction, weight change and hypoglycaemia over the same period.

In Chapter 3 and 4 we demonstrate that simple patient characteristics are associated with response to DPP4 inhibitor therapy, and that simple patient characteristics can identify people with different patterns of response and risk of side-effects with sulfonylurea and thiazolidinedione therapy.

In Chapter 5 we apply joint-longitudinal survival modelling to demonstrate important insights in the association between the benefits (glucose-lowering) and risks (side-effects) of metformin, sulfonylureas and thiazolidinedione therapy.

In Chapter 6 we compare two precision medicine strategies: 1) a recently proposed strategy of using clinical features to assign people with type 2 diabetes into five subgroups; 2) a strategy of using specific continuous clinical features to predict specific outcomes for individual people. We find the strategy using continuous clinical features has greater clinical utility.

Chapter 7 presents an overview of main findings, conclusions, limitations and future work generated by this thesis.

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Abbreviations

ADOPT - A Diabetes Outcome Progression Trial

BMI – Body mass index

CKD – Chronic kidney disease

CPRD - Clinical Practice Research Datalink

DPP4 inhibitor - Dipeptidyl peptidase-4 inhibitor

eGFR – estimated Glomerular Filtration Rate

GAD – Glutamic acid decarboxylase

GLP-1 receptor agonist - Glucagon-like peptide 1 receptor agonist

GoDARTs - The Genetics of Diabetes Audit and Research Tayside Scotland database

HDL-c – HDL cholesterol

HER2 - Human epidermal growth factor receptor 2

HbA_{1c} - Glycated haemoglobin

HOMA2 IR - Homeostatic model assessment insulin resistance

HOMA2 B - Homeostatic model assessment beta cell function

LDL-c – LDL cholesterol

MFN - metformin

NIHR – National Institute for Health Research

NHS – National Health Service

PRIBA - Predicting Response to Incretin Based Agents in Type 2 Diabetes study

RECORD - Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes Trial

SD – standard deviation

SHBG - Sex-hormone binding globulin

SGLT2 inhibitor - Sodium–glucose cotransporter-2 inhibitor

SU - Sulfonylurea

TZD – Thiazolidinedione

UCPCR – Urinary C-peptide creatinine ratio

UK – United Kingdom

US – United States

UKPDS - The UK Prospective Diabetes Study

YODA - Yale University Open Data Access Project

Chapter 1
Introduction

Chapter 1: Table of contents

Part E: Further methodological considerations for evaluating precision medicine in type 2 diabetes

Part F: Data overview

Introduction

Structure

This chapter is divided into 6 sections. Part A states the structure and aims of the thesis. Part B presents an overview of type 2 diabetes and its treatment. Part C presents an overview of precision medicine. Part D discusses the opportunity for a precision medicine approach in type 2 diabetes. Part E outlines key methodological challenges for evaluating precision medicine in type 2 diabetes. Part F introduces the datasets used in subsequent chapters of the thesis.

Introduction part A: Structure and aims of thesis

The overall aim of this thesis is to establish whether clinical patient characteristics are associated with differences in treatment effect for common glucose-lowering therapies, and can inform a precision medicine approach in type 2 diabetes.

Chapter 1 presents an overview of type 2 diabetes and current clinical management, introduce precision medicine and the opportunity for a precision medicine approach in type 2 diabetes, and outline methodological challenges in defining such an approach.

In Chapter 2 we aim to examine recent prescribing patterns in the United Kingdom. We describe recent trends in the prescribing of glucose-lowering therapy, and examine concomitant changes in important short-term patient outcomes including HbA_{1c} reduction, weight change, blood pressure and hypoglycaemia.

In Chapter 3 we examine whether markers of insulin resistance are associated with response to DPP4-inhibitor therapy. This study introduces a key concept of our methodological framework for evaluation of precision medicine: testing the validity of initial findings through replication in independent dataset.

In Chapter 4 we aim to investigate whether simple patient characteristics can identify people with different patterns of response and risk of side-effects with sulfonylurea and thiazolidinedione therapy. This introduces a second key concept: that differences in the benefit of a drug should not be examined without consideration of differences in side-effects.

In Chapter 5 we set out to apply joint-longitudinal survival modelling to directly test associations between the benefits (glucose-lowering) and risks (side-effects) of three widely used glucose-lowering therapies: metformin, sulfonylureas and thiazolidinediones.

In Chapter 6 we aim to test the clinical utility of a recently proposed precision medicine strategy of using clinical features to assign people with type 2 diabetes into five subgroups. We also aim to compare this approach with a strategy of using specific continuous clinical features to predict specific outcomes for individual people.

Chapter 7 is a discussion of the main findings, conclusions, limitations and future work generated by each chapter.

Introduction part B: Type 2 diabetes and its treatment

1.1 Diagnosis of type 2 diabetes

Type 2 diabetes accounts for 90-95% of all diabetes and affects 425 million people worldwide, and over 4 million people in the United Kingdom (UK).(1) Diabetes care is estimated to account for up to 10% of current National Health Service (NHS) expenditure in the UK.(2) Type 2 diabetes is a progressive, multifactorial and heterogeneous condition characterised by chronic hyperglycaemia (raised blood glucose levels). People with type 2 diabetes have varying degrees of lower pancreatic beta cell function (meaning less insulin is produced) and higher levels of insulin resistance. This is in contrast to type 1 diabetes, which is a chronic autoimmune disease characterised by absolute insulin deficiency caused by destruction of the pancreatic beta cells. In usual care in the UK type 2 diabetes is diagnosed using a blood test to measure Haemoglobin A1c (HbA_{1c}), which provides a summary estimate of recent blood glucose levels over an approximately three month period. A HbA_{1c} level of or over 48 mmol/mol (6.5%) is sufficient for diagnosing diabetes, although the test needs to be repeated if the patient does not have any symptoms of diabetes. HbA_{1c} does not identify the type of diabetes, and type 2 diabetes is normally an exclusion based diagnosis, once less common forms such as type 1 diabetes, gestational diabetes, and rare genetic forms of diabetes have been ruled out. .

1.2 The importance of good blood glucose control in type 2 diabetes

Acute symptoms of elevated glucose levels include polyuria, polydipsia, weight loss and dehydration.(3) Long-term consequences of chronic hyperglycaemia

are severe with an increased risk of microvascular complications (neuropathy, nephropathy and retinopathy) and cardiovascular disease, reduced quality of life, and increased mortality.(2)

The majority of people with type 2 diabetes will at some point require drug treatment to lower their blood glucose to prevent symptoms and to reduce their risk of developing diabetes-related complications. The link between improved glycaemic control with glucose-lowering therapy and reduced progression of microvascular complications was first established in the 1990s in the UK Prospective Diabetes Study (UKPDS) study.(4) UKPDS also demonstrated a 'legacy' effect of good early glycaemic control reducing the risk of long-term complications of diabetes.(5)

1.3 Current type 2 diabetes treatment targets recommend an individualised approach

HbA_{1c} levels are the major driver of prescribing decisions for people with type 2 diabetes. UK and the US/European type 2 diabetes treatment guidelines recommend an HbA_{1c} target of 53 mmol/mol (7%) for most individuals.(2, 6) However, guidelines recommend that the HbA_{1c} target is adjusted on an individual basis so as not to impact on quality of life, with the individual target informed by patient preference, patient characteristics (especially comorbidity and frailty), social factors, life expectancy, polypharmacy risks, and risk of adverse drug effects such as side-effects and weight change.(2, 3, 6)

1.4 First-line drug therapy

Metformin is the initial glucose-lowering drug recommended for most individuals in current guidelines, due to its low cost, glucose-lowering efficacy, and safety profile (Table 1).(2, 6, 7) Metformin is however contraindicated in people with

advanced kidney disease (eGFR <30 mL/min/1.73m^2), in this case other drug options are considered (see Section 2.5). UKPDS suggested a mortality benefit for metformin compared with diet alone,(4) although whether metformin reduces risk of cardiovascular disease still remains uncertain.(8)

1.5 Drug options after metformin

As type 2 diabetes is a progressive disease, for many individuals a single agent eventually becomes insufficient to achieve target glycaemic control and additional glucose-lowering therapy is required. In the UK type 2 diabetes treatment guidelines (NICE guidelines) recommend intensification is considered at an HbA_{1c} threshold of 58 mmol/mol (7.5%), although again suggest this should be tailored to individual people.(2)

Additional therapy is added in a stepwise fashion, and when a decision is made to intensify treatment there is now vast choice of drugs after metformin. Three new classes of drug have become available in recent years: glucagon-like peptide 1 (GLP-1) receptor agonists (first agent approved in 2005), dipeptidyl peptidase-4 (DPP4) inhibitors (approved 2006), and sodium glucose co-transporter 2 (SGLT2) inhibitors (approved 2011). These add to the well-established drug classes: sulfonylureas, thiazolidinediones (now only pioglitazone in the UK, although prescribing of rosiglitazone was previously common until around 2010), and insulin. Other drug classes include meglitinides and alpha-glucosidase inhibitors, but these have limited glucose-lowering efficacy and are now rarely prescribed. Each of the major current drug classes recommended after metformin differ in mechanism of action, side-effect profile, and cost (see Table 1 for an overview of common non-insulin options). For glucose lowering, network meta-analysis, including the analysis underpinning NICE guidelines, suggest the average efficacy of most oral

diabetes medications is similar, although head-to-head clinical trials are lacking.(7, 9-11) Durability of glycaemic response is lower with sulfonylureas compared to thiazolidinediones.(12) The ongoing GRADE trial (due 2021) will provide head-to-head long-term comparative effectiveness data for metformin treated participants randomised to sulfonylureas, DPP4 inhibitors, GLP-1 receptor agonists, or insulin, although unfortunately not SGLT2 inhibitors.(13)

1.6 Recent evidence for the cardiovascular benefit of SGLT2 inhibitors and GLP-1 receptor agonists in randomised trials

A major recent development in type 2 diabetes has been clinical trials that have demonstrated a cardiovascular benefit, compared to placebo, for GLP-1 receptor agonists (liraglutide and semaglutide and likely exenatide) and SGLT2 inhibitors (empagliflozin, canagliflozin and likely dapagliflozin) in high-risk individuals with type 2 diabetes and established cardiovascular disease.(14-19) In the main these trials have assessed secondary prevention for participants who have experienced adverse cardiovascular events prior to the trial. Whether the cardiovascular benefit extends to primary prevention of cardiovascular events for individuals at lower cardiovascular risk is unknown.(20) In contrast, for DPP4 inhibitors, similar placebo-controlled cardiovascular outcome trials demonstrated cardiovascular safety but not benefit.(21-23). Evidence of cardiovascular safety or benefit for older therapies is lacking, as cardiovascular safety trials have only been required for new type 2 diabetes therapies since 2008. Prior to this, approval of new drugs was based on demonstration only of glucose-lowering efficacy and safety profile.(24) Of the older therapies, pioglitazone has been shown to have an overall cardiovascular benefit in high-risk individuals compared with placebo, but has been also associated with

Table 1: Overview of major non-insulin glucose-lowering therapies. For further detail see Davies et al. Diabetes Care 2018.(6)

Drug class	Drugs in class	Primary mechanism of action	Major contra-indications	Cost	Weight gain	Common side-effects	Cardiovascular & other effects (see Section 2.6)
Biguanides	Metformin	Decreased hepatic glucose production	Renal disease (eGFR <30)	Low (off-patent)	Limited weight loss	Gastro-intestinal, Vitamin B12 deficiency	Uncertain
DPP4 inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin*	Increased insulin secretion, reduced glucagon secretion	None	High	Weight neutral	Well-tolerated	Cardiovascular safety but not benefit
GLP-1 receptor agonists	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Increased insulin secretion, reduced glucagon secretion, improved satiety	None	High	Weight loss	Gastro-intestinal	Cardiovascular benefit in high-risk people
SGLT2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin	Lowered glucose reabsorption in the kidney so increased urinary glucose excretion	Renal disease (eGFR <45)	High	Weight loss	Genital infections Polyuria Volume depletion Rare: amputation, fracture, DKA	-Cardiovascular benefit in high-risk people -Improvement in blood pressure & renal function
Sulfonylureas	Glibenclamide Gliclazide* Glimepiride Gliplizide	Increased insulin secretion	None (caution required in those for whom hypoglycaemia a particular concern)	Low (off-patent)	Weight gain	Hypoglycaemia	Uncertain
Thiazolidinediones	Pioglitazone Rosiglitazone**	Increased insulin sensitivity	Existing heart failure	Low (off-patent)	Weight gain	Oedema Fracture Heart failure	Pioglitazone: cardiovascular benefit in high-risk people

*not licensed in US for type 2 diabetes **no longer licensed in Europe for type 2 diabetes

increased heart failure.(25) There has been concern that sulfonylureas increase the risk of cardiovascular death compared to other drug classes but no firm conclusions can be drawn from current evidence.(20) A recent unblinded trial found no difference in cardiovascular events between sulfonylureas and pioglitazone, when added to metformin.(26)

1.7 Treatment pathways after metformin – current UK Guidelines

Current UK NICE treatment guidelines leave the choice between drugs after metformin largely to the clinician and patient, making choosing the appropriate therapy a major clinical dilemma. Since 2017, NICE guidelines have recommended 4 oral agents inhibitors as second line therapy options: DPP4-inhibitors, sulfonylureas, pioglitazone and SGLT2 inhibitors.(2) Selection between these drug classes is recommended by matching individual people to the most appropriate therapy for them based on expected treatment effect, (glycaemic improvements, potential side-effects and weight change), patient preferences, comorbidities, polypharmacy risk, and cost.(2)

1.8 Treatment pathways after metformin – current US and European Guidelines

Although US and European treatment guidelines similarly recommend an individualised approach to the selection of therapy after metformin, they have recently been updated to provide more specific recommendations than NICE to match individuals with the most appropriate therapy based on their characteristics.(6) The key change has been that, based on the cardiovascular benefit shown in trials, these guidelines now recommend SGLT2 inhibitors and GLP-1 receptor agonists as add-on therapy for individuals who are over their HbA_{1c} target and have established cardiovascular disease. This criteria would

apply to around 15-20% of people with type 2 diabetes.(6, 27) For the remainder of individuals, patient preference, comorbidities, glycaemic control, side-effects (in particular risk of hypoglycaemia), weight change and cost remain the key considerations.(6) Specific updates in the recent guidelines around these include: 1) the recommendation for use of SGLT2 inhibitors (empagliflozin or canagliflozin) in people with established chronic kidney disease (CKD), as they may slow progression of CKD;(28) 2) the avoidance of sulfonylureas if there is a need to minimise hypoglycaemia; 3) the use of SGLT2 inhibitors or GLP-1 receptor agonists if weight control is a priority; 4) the use of sulfonylureas or thiazolidinediones in settings where cost is the major issue.(6)

1.9 Third-line intensification and beyond

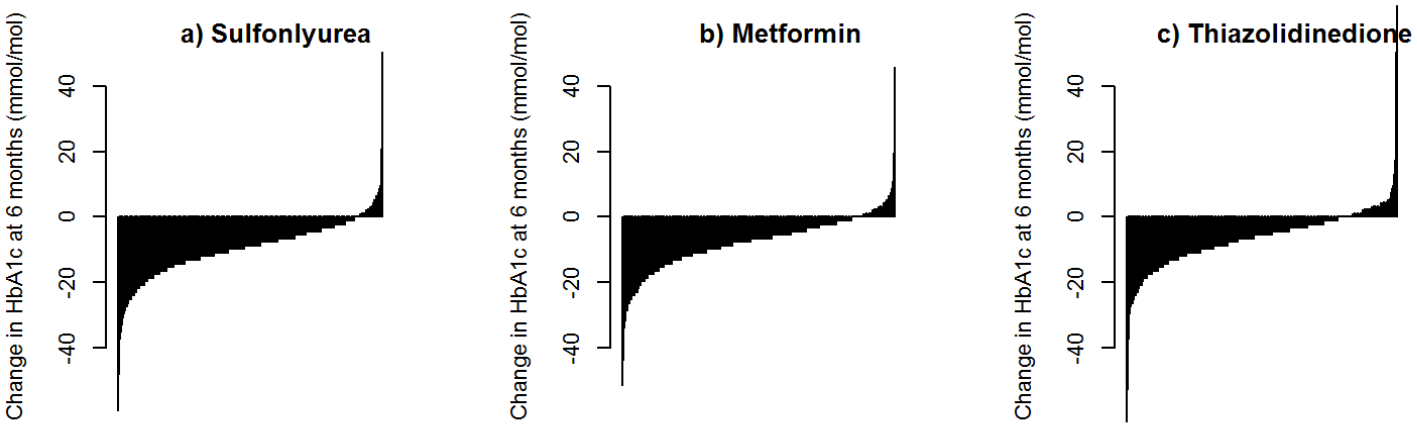
Treatment selection for further therapy intensifications follow the same general selection process as for second-line therapy, with insulin also considered. In the UK NICE guidance a key difference with the recent US/European guidelines is that GLP-1 receptor agonists are currently recommended only in individuals with BMI ≥35 kg/m², and at the earliest third-line.(2) NICE also recommend that GLP-1 receptor agonists are stopped at 6 months unless an individual has a HbA_{1c} reduction of at least 11 mmol/mol (1%) and weight loss of at least 3%.(2)

1.10 Guidelines reflect differences in average treatment effect, not differences between individuals in treatment effect

Current guidelines highlight the importance of an individualised approach to selecting treatment, including a focus on likely treatment effectiveness.(2, 3, 6) However, estimates of treatment effectiveness are currently informed only by average effect sizes observed in clinical trials, rather than expected differences in treatment effect between individual people. Despite this, trials have shown

there is substantial variability between people in glucose-lowering response to therapy.(29) Similarly, only some people develop side-effects. An example of the large variability between individual people in glucose-lowering is shown in Figure 1. Blood glucose (HbA_{1c}) is lowered for most people, but some individuals appear to have a marked response to a drug, whilst for other individuals there appears to be little or no therapeutic response. Such inter-individual variability is widely thought to represent true heterogeneity in treatment response between people, and as a result to have great clinical relevance.(29) However, the degree to which this heterogeneity differs for different drug classes or relates to the underlying characteristics of people with type 2 diabetes is largely unknown.(30) A key knowledge gap identified in guidelines has been whether the comparative effectiveness and safety of the different drug options varies by simple patient characteristics.(7)

Figure 1: Distribution of individual changes in HbA_{1c} at 6 months (6 month HbA_{1c} minus baseline HbA_{1c}) by drug in ADOPT randomised trial for 3,707 participants with a measure of HbA_{1c} at 6 months) (Dennis, Jones unpublished). Mean (standard deviation) improvement in HbA1c was greatest at 6 months for sulfonylureas -9.4 (8.6) mmol/mol [-0.9% (0.8%)], compared to



metformin -7.5 (8.1) mmol/mol [-0.7% (0.8%)] and thiazolidinedione therapy -6.4 (8.6) mmol/mol [-0.6% (0.8%)], although for each drug there was a large variability between individuals in change in HbA_{1c}.

1.11 Conclusions

Choice of therapy after metformin when additional therapy is required to lower blood glucose levels is a major clinical dilemma for most people with type 2 diabetes. Recent evidence of cardiovascular benefit with SGLT2 inhibitors and GLP-1 receptor agonists supports their use after metformin, but only for the relatively small proportion of high-risk people with established cardiovascular disease. This means that for the majority of people with type 2 diabetes likely treatment effect (glucose-lowering effect and risk of side-effects) remain an important consideration when choosing therapy, alongside consideration of patient preference, comorbidities, polypharmacy risk, and cost.

Although average glucose-lowering of oral medication options after metformin is similar, there is known to be wide variability in treatment effect between individual people. It is unknown whether this variability has clinical utility. Similarly, although drugs are known to differ in side-effects, it is largely unknown to what extent individual people differ in risk of developing side-effects on specific therapies. As a result current guidelines and treatment decisions are based on estimates of average treatment effects for the different drug options, rather than estimates of likely differences in treatment effect between individuals.

Introduction part C: Overview of precision medicine

This section will introduce precision medicine and present examples of two successful applications of precision medicine in other diseases.

1.12 Definition of precision medicine

Precision medicine can be defined as the “targeting of treatment according to the biological or risk characteristics shared by people.”(31) The term precision is often used interchangeably with personalised or stratified medicine, although stratified medicine more typically refers to attempts to identify discrete subgroups of individuals rather than the targeting of treatment at the individual level.(32)

Precision medicine aims to provide more tailored predictions of likely treatment effects for individual people or subgroups of people based on their genotypic or phenotypic characteristics, in contrast to the present “one size fits all” approach common for most diseases. The hope is that more accurate information on likely treatment effects will improve clinical decision making, maximising the potential benefit from treatment whilst minimising the potential harm.

1.13 Successful applications of precision medicine

The NHS England 2016 strategy highlighted the potential benefits of a precision medicine approach.(33) However, despite widespread interest, there have been relatively few clinically relevant applications of precision medicine to date. Two successful implementations in cancer and rare forms of diabetes are outlined below. Key to the success of both these precision medicine strategies has been

the identification of discrete disease subtypes which can then inform treatment for individual people. The clinical efficacy of the precision medicine approach has then been demonstrated in prospective clinical trials.

1.13.1 Application of precision medicine in cancer

Precision medicine is now widely used in cancer where testing of malignant tissue for genetic mutations, expression or biomarkers can be used to reveal heterogeneity and identify discrete subtypes, rather than just the broad cancer type.(34) These subtypes can then be treated differently, with improved outcomes. A clear example is HER2 positivity in breast cancer. Data from multiple randomised control trials have shown that the 15-20% of people with HER2 positivity (HER2 protein overexpression) can be selected for treatment with HER2-directed drugs, which leads to marked improvements in disease-free survival.(35)

1.13.2 Application of precision medicine in rarer types of diabetes

A second successful application of precision medicine has been in monogenic and neonatal diabetes.(36) 2.5% of children with diabetes have monogenic diabetes.(37) Precise etiological subtypes of monogenic diabetes have been identified based on the underlying genetic aetiology. The most common genetic mutation is in HNF1A, and an important study demonstrated that individuals with this monogenic subtype differs in treatment response, having a marked sensitivity to sulfonylureas meaning they can be taken off insulin and maintain good blood-glucose control with sulfonylurea tablets.(36) Similarly, in neonatal diabetes due to KCNJ11 mutations, sulfonylureas have been shown to restore insulin secretion,(38) again meaning individuals can be treated long-term with

these tablets instead of insulin with improved long-term glycaemic control.(39, 40)

Introduction part D: The opportunity for a precision medicine approach in type 2 diabetes

1.14 The potential for a precision medicine approach in type 2 diabetes

Type 2 diabetes glucose-lowering therapy is an excellent candidate for a precision medicine approach for the following reasons: 1) There are many different medication options after metformin with different mechanisms of action but the same principal aim: to lower blood glucose; 2) Current treatment guidelines do not provide information which medication is best for lowering glucose, for which people; 3) There is great heterogeneity in clinical presentation of type 2 diabetes. This makes it plausible people with different underlying pathophysiology will vary in response to the different drug classes, and vary in susceptibility to side-effects, depending on the mechanism of action of the drug; 4) At the individual level glucose-lowering response and susceptibility to side-effects appears to vary greatly.

Despite this, a precision medicine approach to select therapy based on assessment of individual or subgroup level characteristics, rather than broad differences between drugs, is not close to implementation in type 2 diabetes clinical care. The next sections outlines potential strategies for developing a precision medicine approach in type 2 diabetes.

1.15 Precision medicine based on defining discrete subtypes of type 2 diabetes will be difficult

Any successful implementation of precision medicine in type 2 diabetes is likely to be very different to those established in cancer and other forms of diabetes. Unlike cancer, tissue is not available for testing, and unlike rare forms of diabetes, type 2 diabetes genetic testing does not allow clear definition of the underlying pathophysiology. This makes identification of discrete, non-overlapping subtypes of type 2 diabetes with different treatment requirements much less likely.(41)

Several approaches based on assigning individuals with type 2 diabetes into subgroups have however recently been proposed.(42-45) Most notable of these is a recent data-driven cluster analysis of Scandinavian registry data, which based on three routine clinical measures (HbA_{1c}, BMI, and age at diagnosis) and three non-routine measures (GAD autoantibody positivity and HOMA-measures of beta-cell function (HOMA2-B) and insulin resistance (HOMA2-IR)),(46) identified five reproducible ‘novel subgroups’ of newly diagnosed adult diabetes, four of which represent a potential subclassification of type 2 diabetes.(42) Although the clusters appeared to differ in risk of complications in observational follow-up, most notably diabetic kidney disease, a key point is that the clusters are non-discrete. This means they overlap in terms of their clinical characteristics. Although the potential clinical utility of the clusters to select glucose-lowering therapy was suggested in the original study, there was no evaluation of whether the clusters differed in treatment response with different drugs.(42) Similarly, the clinical utility of the other recent cluster-based approaches has not been assessed, or compared with alternative precision

medicine approaches that do not assign individuals into subgroups.(43-45, 47, 48)

1.16 Precision medicine based on identifying variation between people in treatment effect for specific drug options

An alternative precision medicine approach is, instead of attempting to assign people into subtypes of type 2 diabetes based on pathophysiology, to attempt to match individuals or subgroups with the drug with which they are likely to have the greatest glucose-lowering response and/or least risk of side-effects.(49) This requires demonstration of robust and clinically relevant differences in treatment effect between people with different underlying characteristics.

There are several ways that this approach can be developed and tested. One way would be to design prospective clinical studies designed specifically to evaluate precision medicine, by assessing potential markers of differential response to different drug classes. An example is the ongoing TRIMASTER trial which is testing two hypotheses: 1) that a subgroup of individuals with BMI>30 will, compared to a subgroup with BMI<30, have a greater response to the thiazolidinedione pioglitazone and a lesser response to the DPP4 inhibitor sitagliptin; 2) that a subgroup of people with reduced renal function (eGFR 60-90) will, compared to a subgroup with eGFR>90, have greater response to sitagliptin but a lesser response to the SGLT2 inhibitor canagliflozin.(50) The principal disadvantages of such prospective trials are the considerable time and expense required. A further limitation of TRIMASTER is the fact only one clinical characteristic at a time is used to define the subgroups.

In comparison, existing data resources such as individual-level patient data from existing clinical trials, and data from routine medical care (see Introduction:

Section 6) may provide a more cost-effective and practical opportunity to evaluate precision medicine in type 2 diabetes. The next two subsections describe two possible approaches to evaluate differences in glucose-lowering response. Only the second approach is likely to provide useful information using standard trial and routine care datasets.

1.16.1 Identifying true "responders" or "non-responders" to glucose-lowering therapy is not possible with currently available data

This strategy would aim to use the variability between people in glucose-lowering response to therapy (Figure 1) to define individual "responders" or "non-responders" by applying clinically relevant HbA_{1c} cut-offs (for example, responder defined as individuals with ≥0.5% HbA_{1c} improvement, non-responder defined as <0.5% HbA_{1c} improvement). Differences in characteristics between responders and non-responders could then be examined. However, Stephen Senn has demonstrated that identifying 'true' responders or non-responders in this way at the individual-level is not possible in standard parallel-arm randomised controlled trials, which are designed only to compare average differences in outcome between the treatment arms (the variation between treatments averaged over all people).(51, 52) The same issue applies in observational datasets. The reason is that it is not possible to separate the variation of interest (person by treatment variation in the degree of change in HbA_{1c} i.e. heterogeneity in treatment effect or different people responding differently to the same specific drug) from two further sources of variation; 1) between person variation (the variation in response between people that would occur irrespective of the drug given; 2) the within person error (the variation from occasion to occasion when the same person is given the same treatment) (Table 2).(51, 52) This means that the apparent variability between people in

glucose-lowering response observed in Figure 1 may in fact not represent true heterogeneity in treatment effect. Separating the sources of variation and identifying true responders or non-responders requires multi-period crossover trial designs where participants are randomised to two-or-more therapies at least twice. Only this design allows separation of the variation of interest: treatment by person interaction.(51-53) Multi-period cross-over trials are rare in medicine and have not yet been conducted in type 2 diabetes.(32)

Table 2: Sources of variation in treatment response (Adapted from Senn)(52)

Type of variation	Definition
Between treatments	The variation between treatments averaged over all people (standard outcome tested in a trial)
Between people	The variation between people that would occur irrespective of the treatment given
Treatment by person interaction	The extent to which the effect of treatment varies from person-to-person
Within person	The extent to which the effect of treatment varies from occasion to occasion when a person is given the same treatment

1.16.2 Evaluating whether patient characteristics are associated with glucose-lowering response to therapy is possible with currently available data

It is however possible to use standard parallel-arm trial and observational datasets to evaluate whether true, predictable differences in response to the different therapy options in type 2 diabetes exist. What is required is the demonstration of associations between clinical features and response at the subgroup level (for example demonstrating that response is different in males

and females). By focusing on the subgroup-level, rather than individual-level, other people in the subgroup provide the replication required to establish the presence of subgroup by treatment variation. The same interpretation can be made for associations between continuous patient features (e.g. BMI) and treatment effects. If a clinical feature can be identified that has different associations with response with different drugs (for example if response to Therapy A is different in males and females, but there is no difference in response by sex for Therapy B), this may provide evidence of patient by drug variation that can inform a precision medicine strategy, although consideration should also be given to alternative explanations such as differences between individuals or subgroups in treatment inertia or in medication adherence. If a clinical feature is associated with greater or lesser response to a similar degree for all drugs, this provides evidence of between patient variation rather than patient by treatment variation, and the feature is not likely to be useful to target therapy. Features associated with outcomes irrespective of treatment are commonly termed “prognostic” factors.(31, 54)

In summary, the basis of the approach detailed in this section is identification of patient-level characteristics that robustly and consistently predict differential glucose-lowering response across the different drug options. Most useful will be characteristics associated with greater response to one drug but lesser response to another drug, although characteristics associated with response to one or more drugs but not others will also have utility. Only such differential factors offer the potential to provide useful information to select the most effective treatment for individuals and inform a precision medicine approach in type 2 diabetes.

1.17 Evidence for differential response to glucose-lowering agents

Although establishing whether there are true differences between individuals in treatment response to the different glucose-lowering agents has been identified as a key area for future research, there is limited robust evidence in this area; many of the studies that have been conducted are small in size, have methodological limitations, and lack replication.(7, 41, 55, 56) Clinical drug efficacy trials are focused on average treatment effects and are severely underpowered for evaluating heterogeneity in treatment effects between subgroups (see Section 3.2 for an overview of the limitations of classical subgroup analysis in clinical trials).(57) This means the subgroup analyses commonly reported in clinical trials provide little credible evidence to evaluate the potential for a precision medicine approach to type 2 diabetes therapy.

The following two subsections present an overview of the most robust current evidence from studies specifically designed to evaluate clinical features and genetic factors associated with glucose-lowering response to type 2 diabetes therapies.

1.17.1 Clinical patient features associated with drug response

Angus Jones and colleagues recently showed in the prospective Predicting Response to Incretin Based Agents in Type 2 Diabetes (PRIBA) study that reduced glucose-lowering efficacy of GLP-1 receptor agonists was associated with clinical markers of low beta cell function such as lower C-peptide and longer duration of diabetes in insulin-treated people.(58) It is not known whether these findings are applicable to non-insulin treated individuals, or if the same factors predict response to DPP4 inhibitors, the drug class with a similar glucose-lowering mechanism of action. A systematic review of studies

published prior to the PRIBA analysis did not clearly identify any factors associated with glycaemic response to either DPP4 inhibitors or GLP-1 receptor agonists except baseline HbA_{1c}.(59) Lower BMI, lower insulin resistance and Asian ethnicity were however associated with greater response to DPP4 inhibitors in some studies. The review noted substantial weaknesses in the methodology of previous work, including a lack of adjustment for baseline HbA_{1c} in many studies (see Section 5.1.2).

An early observational analysis of the association between BMI and glucose-lowering response with sulfonylureas and metformin in UK primary care data suggested that higher BMI was associated with a lesser glucose-lowering response with metformin but that the effect size did not reach clinical significance (mean decrease in HbA_{1c} for obese individuals 14.6 mmol/mol (1.4%); non-obese individuals 15.9 mmol/mol (1.5%)).(60) There was no evidence of an association for sulfonylureas. A more recent observational study again using UK primary care data found differences in response between sulfonylureas and thiazolidinediones, with greater glucose-lowering with thiazolidinediones in obese females.(61)

Baseline HbA_{1c} is the major predictor of glucose-lowering response for all drug classes, with a higher baseline HbA_{1c} associated with a greater HbA_{1c} response if defined as absolute change from baseline HbA_{1c} (see Section 5.1.1 for further discussion of this point).(62-65) A number of studies have examined whether HbA_{1c} and glucose-lowering response differ by drug class and generally shown only modest differences between drug,(62, 65-67) although post-hoc analysis of two head-to-head trials have recently suggested there may be greater relative benefit with the SGLT2 inhibitor empagliflozin at higher baseline HbA_{1c} levels compared to the DPP4 inhibitor sitagliptin and sulfonylurea glimepiride.(68)

1.17.2 Genetic associations with drug response

A recent review found over 120 studies evaluating gene-drug interactions in diabetes, with potential pharmacogenetic influences on glucose-lowering response in type 2 diabetes reported for metformin, sulfonylureas and thiazolidinediones.(69-73) However, the majority of studies have been small in size and lacked replication.(41) Several associations have been replicated in multiple independent studies, notably CYP2C9 and TCF7L2 variants for sulfonylureas and ATM for metformin (in some, but not all, populations), but the size of glucose-lowering effect has been relatively small.(49, 69) Very little is known about pharmacogenetic influences on glycaemic response for the newer drug classes DPP4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists.(41) Given the high prevalence of type 2 diabetes, the cost of genetic testing, and the small effect sizes reported, the main utility of pharmacogenetics may well be in better understanding the underlying mechanisms by which the different drug classes influence glycaemic control, rather than for informing a precision medicine approach based on drug response. Genetic testing is more likely to be cost-effective if, instead of differences in drug response, it can identify people who are likely to derive particular cardiovascular benefit from specific therapies.

1.18 Evidence for differences between people in risk of side-effects

Few studies have systematically evaluated whether patient characteristics influence the risk of developing common drug specific side-effects. With thiazolidinediones, it has been established that bone fractures are more common in post-menopausal females.(74) Older age has long been considered to be a risk factor for hypoglycaemia with sulfonylureas,(75) although trials have

shown older people can be safely treated with these agents.(76, 77) Similar approaches to those outlined above for glucose-lowering response will be required to evaluating the potential for a precision medicine approach to guide therapy based on individualised risk of side-effects.

1.19 Evidence for differences between people in cardiovascular risk

Subgroups of people with type 2 diabetes and established cardiovascular disease have been shown to have a cardiovascular benefit with SGLT2 inhibitors and GLP-1 receptor agonists in placebo-controlled trials (see section 2.6), although it is unclear whether this benefit extends to lower-risk people. It is also unknown whether older agents such as sulfonylureas would show similar or different effects if equivalent trials were conducted. Although simple subgroup analysis has been conducted within the trials, it is uncertain to what extent the cardiovascular benefit of SGLT2 inhibitors and GLP-1 receptor agonists may vary by participant characteristics. Similarly, as these agents are relatively new, there are limited follow-up data in primary care to evaluate ‘real-world’ differences between people in cardiovascular outcomes.

1.20 Conclusion

There may be great potential to apply a precision medicine approach to select therapy for people with type 2 diabetes. Available drug options differ in mechanism of action and known side-effects, and at the individual-level there appears to be marked heterogeneity in treatment effect, in particular in glucose-lowering response. If this apparent individual-level variation in treatment effect relates to underlying patient characteristics this could allow different drugs to be targeted to those most likely to benefit: a precision medicine approach. Although identifying true responders or non-responders to specific medications requires complex prospective trial designs, existing data (such as completed trial and observational datasets) offer the potential to evaluate associations between patient level characteristics and treatment effects with the different drug options.

Current evidence supporting a precision medicine approach in type 2 diabetes is limited, and many studies reporting associations with response lack replication. Studies to date suggest the use of routine patient features, rather than genetic testing, is likely to provide the most practical way in which a precision medicine approach can inform selection of glucose-lowering therapy in clinical practice.

Introduction part E: Further methodological considerations for evaluating precision medicine in type 2 diabetes

Methods to evaluate precision medicine approaches are not well-established. This section will provide an overview of considerations and challenges most relevant to evaluating a precision medicine approach to type 2 diabetes therapy.

1.21 Modelling glucose-lowering response

1.21.1 Definition of glucose-lowering response

Glucose-lowering (glycaemic) response after starting therapy in diabetes is commonly defined in two ways in research studies. The first is whether an individual achieves a specified target HbA_{1c} threshold (a binary outcome). The second is an individuals' HbA_{1c} change from baseline (a continuous outcome). Previously, Jones and colleagues have shown that these different definitions of response identify very different individuals as good responders to therapy (when good responders are defined as the top quartile of responders to each therapy under each definition).(78) This difference is due to the influence of baseline HbA_{1c}.(78) Compared to individuals with high baseline HbA_{1c}, people with a low baseline HbA_{1c} are more likely to reach a target HbA_{1c} threshold but are likely to have a lesser HbA_{1c} change (a floor effect).

HbA_{1c} change is the more appropriate outcome for studies evaluating a precision medicine approach to therapy. The main drawback of using a

threshold is that arbitrarily dichotomising a continuous variable such as HbA_{1c} into two groups will result in substantial loss of statistical power to detect associations between baseline clinical features and response.(79, 80)

1.21.2 Adjustment for baseline HbA_{1c}

Baseline HbA_{1c} is strongly associated with response to glucose-lowering therapy,(62-64) and has been estimated to account for 36% of variability in HbA_{1c} change from baseline irrespective of therapy (meta-analysis of 59 clinical trials: weighted R^2=0.36).(62) Baseline HbA_{1c} is therefore a major potential confounder when evaluating association between response and clinical features which are themselves likely to be correlated with baseline HbA_{1c}, such as BMI and lipids. This suggests adjustment for baseline HbA_{1c} is the appropriate strategy. However, adjustment for baseline has been shown to increase bias in certain cases in other fields, in particular when the association between baseline and response is largely explained by regression to the mean.(81) Jones and colleagues have recently assessed the impact of regression to the mean when evaluating type 2 diabetes treatment response, and showed that the effect of regression to the mean is relatively small compared to the true effect of baseline HbA_{1c} on response.(64) Failure to adjust for baseline HbA_{1c} led to associations between markers strongly associated with baseline HbA_{1c} and response that bias adjustment suggested were likely to be false.(64) This study strongly suggests that adjustment for baseline HbA_{1c} to evaluate potential predictors of response in studies of precision medicine in diabetes is both necessary and appropriate.

1.21.3 Choice of time point for evaluating glycaemic response

Glycaemic response is known to vary over time with different type 2 diabetes drug classes. In particular, in randomised trials sulfonylureas have been shown to have a greater initial response but less durable response than metformin and thiazolidinediones,(12) and the SGLT2 inhibitor canagliflozin.(82) Initial response is more likely to reflect the 'pure' pharmacological action of the drug, whilst long-term response is likely to reflect both pharmacological action and underlying disease progression. The extent to which choice of time point may influence findings in studies evaluating predictors of treatment response in type 2 diabetes is unknown.

1.22 The pitfalls of classical subgroup analysis to evaluate heterogeneity in treatment response

The conventional approach to evaluate heterogeneity in trials is to examine differences in outcomes across large numbers of exploratory participant subgroups defined on the basis of single characteristics (e.g. sex) or by dichotomising continuous baseline measures (e.g. BMI </≥30).(83) Even when pre-specified in trial protocols, such analyses are typically severely underpowered as trials are powered only for the main effect, leading to the potential of false negative findings.(57, 84, 85) Trials with 80% power for the main effect have been estimated to have only 29% power to detect a subgroup effect of the same magnitude.(86) When multiplicity-adjusted significant associations have been observed these have been shown to be rarely validated in subsequent studies, suggesting they may be false positives.(84, 87) These studies suggest that classical, hypothesis-free, subgroup analysis is unlikely to the most efficient approach to evaluate whether differential treatment response to type 2 diabetes therapy exists. Although superior to subgroup analysis,

testing interactions between continuous features and treatment response in trial data will still be underpowered.(84)

1.23 Evaluation of multiple patient outcomes: the association between the benefits and risks of therapy

A key but often overlooked question in precision medicine is: are the risks of a drug positively correlated with the benefits?(84) For glucose-lowering therapies, the relevant question is whether people with characteristics favouring good glycaemic response to a specific drug are also at increased risk of drug specific side-effects. This will be more likely if side-effects relate to the mechanism of action of the drug. A positive association may limit the clinical utility of a precision medicine approach in type 2 diabetes based on likely glucose-lowering.

Risk-benefit analysis has been suggested to evaluate associations between benefits and harms for precision medicine, but there have been no studies in type 2 diabetes and there have been few practical applications in other diseases.(84, 88, 89) It has been proposed that risks are reported at the same level as the benefits (for example if benefits are reported at subgroup level so should the risks).(84) However, no framework or modelling strategy has been proposed to directly evaluate potential associations between the benefits and risks of drug therapy. One potential strategy for precision medicine in type 2 diabetes would involve directly testing the association between the HbA_{1c} response to a drug over time (a longitudinal outcome) and the risk of developing a side-effect (a survival outcome).

1.24 Strengths and weaknesses of available datasets to evaluate precision medicine in type 2 diabetes

1.24.1 UK primary care data

UK population based primary care databases, such as Clinical Practice Research Datalink (CPRD),(90) contain the anonymised routinely collected primary care records of consenting individuals registered with a broadly representative sample of general practices.

UK primary care records provide several potential advantages for study of a precision medicine approach in type 2 diabetes. Primary care databases reflect ‘real-world’ prescribing with no inclusion criteria, providing complete data on prescriptions issued (although no data on drug dispensation), and thus enabling head-to-head evaluation of all diabetes drugs currently used in clinical practice. Large sample size reduces concern about power when evaluating subgroups or predictors of response to patient outcomes. Pay-for-performance targets (introduced in 2004 through The Quality and Outcomes Framework (QOF)) have resulted in consistent high-quality clinical data entry about chronic disease, with incentivised annual monitoring of HbA_{1c} levels in people with type 2 diabetes.

There are however significant limitations to the use of primary care data to evaluate differential treatment effects. The counterpoint to increased power from increased sample size is the risk of overly precise results and false positive findings. Biases in prescribing behaviour, in particular selective prescribing based on disease severity or prognosis (prescribing by indication), may limit head-to-head comparisons of different drug classes. If the reason underlying the prescribing decision is unrecorded in the primary care system

standard analytical approaches cannot remove this systematic bias.(7) For comparison of drug-specific side-effects there is also likely to be recording bias. This will be present if clinicians are more likely to record a side-effect for people on a specific drug known to cause the side-effect, but are less likely to record the same side-effect if it occurs in people treated with other drugs. A further related weakness is missing data, which as primary care data is not collected for research is substantial. Analysis of only the subset of people with complete data (complete-case analysis) will be biased if people with missing data differ systematically to those with complete data.(90)

A further confounder relevant for studies of precision medicine but not easily measured in primary care data is adherence to medication. Information on prescriptions issued is captured in the primary care record but no data are available on whether prescriptions were collected or medication was taken as prescribed. The medication possession ratio is a commonly used approach to estimate adherence in primary care records from prescriptions issued, and has been defined as the “number of days of available medication divided by the number of days between the first and last prescription dates, multiplied by 100.”(91) Farmer and colleagues showed that reduced adherence is common in primary care (13% of CPRD people), varies by medication class, and is associated with smaller reductions in HbA_{1c}.(91)

1.24.2 Existing randomised clinical trial data

Individual participant-level data from completed clinical trials are increasingly available upon application for researchers to answer secondary research questions. Data access portals include Clinical Study Data Request and The Yale University Open Data Access (YODA) Project.(7, 92)

A current topic of debate is how best to use such existing clinical trial datasets,(93-96) the majority of which are drug efficacy trials. Type 2 diabetes randomised trial data have an advantage for evaluating predictors of response and side-effects to specific agents compared with observational data, as confounding is greatly reduced through randomisation. Further advantages are the availability of protocol-driven follow-up of both HbA_{1c} and other clinical measures in participants randomly assigned to therapy, and the capture of standardised information on the occurrence of side-effects. However, there are important limitations to consider. These include a potential lack of representativeness due to trial inclusion criteria (for example people with high HbA_{1c} values are typically excluded at screening), which might limit generalisability. A second key limitation for evaluating precision medicine is the fact there are relatively few head-to-head trials of current agents; the majority of efficacy trials are placebo controlled. This makes evaluating whether clinical factors are associated with response to a specific drug, or to all drugs, more challenging. Finally, as discussed in Section 5.2, trials are likely to be underpowered to detect drug by subgroup or drug by continuous measure interaction effects, and principled approaches to evaluate candidate markers are required as “post-hoc observations should be treated with scepticism.”(97)

1.25 Triangulation using primary care and clinical trial datasets

The different strengths and weaknesses of primary care and clinical trial data suggest the potential for a ‘triangulation’ like approach to evaluate precision medicine in type 2 diabetes.(97, 98) An example where this has been successfully applied include research to establish the causal effect of lower systolic blood pressure and coronary heart disease risk, for which prospective cohort, genetic, and randomised trial data were compared.(99) Each of these

data sources have different biases and assumptions, and the demonstration of broadly consistent results increases confidence a true causal effect has been measured; in this case that lower systolic blood pressure reduces coronary heart disease risk. A further example is the use of prospective cohort studies, within-sibling studies and randomised trial data to establish there is unlikely to be a link between being breastfed and later life BMI. For precision medicine in type 2 diabetes,(98) the emphasis of a triangulation approach would be to test the reproducibility of associations between patient characteristics and treatment effects across trial and observational datasets from different sources. Demonstration of robust and reproducible associations in this way will greatly strengthen the credibility of any proposed precision medicine strategy based on clinical features.

1.26 Conclusions

Recent work has provided important information to inform study of a precision medicine approach in type 2 diabetes, although important methodological challenges remain. There may be great potential to use routine primary care and clinical trial datasets to evaluate predictors of glucose-lowering response and risk of side-effects for the different glucose-lowering therapy options. However, both primary care data and trial data have important limitations, and a key question is how to effectively harness both data sources to study precision medicine.

Introduction part F: Data overview

This section provides an overview of the different datasets used in subsequent chapters of the thesis. Both routine and trial datasets were used, enabling a triangulation-based approach, with replication of analyses in different datasets to strengthen the credibility of findings.

1.27 Routine clinical data

1.27.1 Clinical Practice Research Database (CPRD)

CPRD was established in 1987 and is one of the world's largest longitudinal general practice research databases.(90) CPRD is broadly representative of the wider UK population. The anonymised database of electronic health records includes demographic information, clinical diagnoses, symptoms, laboratory test results, primary care issued prescriptions, process of care codes (e.g. specialist referrals), and clinical measurements (e.g. body mass index (BMI)). As of mid-2013 there were over 11.3 registered people (4.4 million actively registered) from 674 general practices across the UK.(90) CPRD has been used upwards of 2000 retrospective research studies (CPRD, unpublished), and people with type 2 diabetes have been widely studied using CPRD.(100) CPRD was used for this research as it provides comprehensive clinical records for over 400,000 people with type 2 diabetes in the UK, including information on their sociodemographics, laboratory results including HbA1c, prescriptions issued, and occurrence of side-effects while taking medication.

1.27.2 The Genetics of Diabetes Audit and Research Tayside Scotland database (GoDARTs)

The Genetics of Diabetes Audit and Research Tayside Scotland database (GoDARTs) has been used extensively to study the epidemiology and pharmacoepidemiology of diabetes.(73) Similarly to CPRD, data are captured as part of routine clinical care. Data are available for around 10,000 people with diabetes from 1992 onwards. GoDARTs was used for this research to provide an independent “real-world” dataset with information on prescribing and outcomes to validate findings in CPRD.

1.28 Individual-level participant data from randomised clinical trials

1.28.1 A Diabetes Outcome Progression Trial (ADOPT)

ADOPT (2000-2006) was a double-blind randomised trial designed to compare long-term blood glucose control (glycaemic durability) with thiazolidinedione (rosiglitazone), metformin and sulfonylurea (glibenclamide) therapy.(101) Participants were drug-naïve and close to diagnosis of type 2 diabetes. Participants were 88% Caucasian. 4,351 participants were randomised and received study medication, and over a median follow-up of 4 years the trial showed much greater glycaemic durability with thiazolidinedione therapy over the comparator drugs.(12) Data on HbA_{1c} levels, other clinical measures such as weight change and kidney function, and occurrence of side-effects were recorded as part of protocol driven follow-up. ADOPT was used for this research as it provided blinded, randomised glycaemic outcome data for two of the four therapies recommended second-line in current guidelines (SUs and TZDs), making it the ideal dataset to validate findings on glycaemic response and side-effects from CPRD in controlled conditions.

1.28.2 Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial

RECORD (2001-2008) was a randomised trial designed to compare cardiovascular outcomes in participants adding a thiazolidinedione (rosiglitazone) to either metformin or sulfonylurea therapy, compared to participants moving onto metformin and sulfonylurea dual-therapy.(102) Participants were 99% Caucasian. In contrast to ADOPT, RECORD was an open-label rather than double blinded trial. Similarly to ADOPT, data on HbA_{1c} levels, other clinical measures, and side-effects were recorded in protocol

driven follow-up. 4,447 participants were randomised and followed up for a mean 5.5 years.(103) Although there was no difference in the primary outcome (cardiovascular hospitalisation or cardiovascular death), there was an increased risk of heart failure and fracture with thiazolidinedione therapy compared to the comparator drugs. RECORD was used for this research to provide a further trial replication dataset.

1.29 Predicting Response to Incretin Based Agents in Type 2 Diabetes (PRIBA) prospective study

PRIBA (2011-2014) was a prospective study of 957 participants designed to evaluate the relationship between measures of insulin secretion (as measured by blood C-peptide or Urinary C-peptide Creatinine Ratio (UCPCR)) and insulin resistance on glucose-lowering response in participants starting DPP4 inhibitors and GLP-1 receptor agonists as part of their usual diabetes care in the UK.(104) For GLP-1 receptor agonists, lower values of both C-peptide and UCPCR were associated with reduced glycaemic response at 6 months.(58) PRIBA was used for this research as it is one of the very few prospective cohort studies specifically designed to test a precision medicine hypothesis. Results from PRIBA for participants initiating DPP4 inhibitors have not yet been reported.

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Chapter 2

Time trends in prescribing of type 2 diabetes drugs, glycaemic control and risk factors: a retrospective analysis of primary care data, 2010-2017

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Acknowledgments of co-authors and contributions to paper

I conceived the idea for the study. Andrew Hattersley, Beverley Shields, Angus Jones and I designed the study. Beverley Shields and I prepared and analysed the data. I drafted the manuscript, with assistance from Beverley Shields and Angus Jones. All authors provided support for the interpretation of results, critically revised the manuscript, and approved the final draft of the manuscript.

Abstract

Aim

Prescribing in type 2 diabetes has changed markedly in recent years, with increasing use of newer, more expensive glucose-lowering drugs. We aimed to describe population-level time trends in both prescribing patterns and short-term clinical outcomes (HbA_{1c}, weight, blood pressure, hypoglycaemia and treatment discontinuation) after initiating new therapy.

Methods

We studied 81,532 UK people with type 2 diabetes initiating a first to fourth line drug in primary care between 2010-2017 inclusive (Clinical Practice Research Datalink). Trends in new prescriptions and subsequent six and twelve-month adjusted changes in glycaemic response (reduction in HbA_{1c}), weight, blood pressure, and rates of hypoglycaemia and treatment discontinuation were examined.

Results

DPP4 inhibitor use second-line near doubled (41% of new prescriptions in 2017 vs. 22% 2010), replacing sulfonylureas as the most common second-line drug (29% 2017 vs. 53% 2010). SGLT2 inhibitors, introduced in 2013, comprised 17% of new first-fourth line prescriptions by 2017. First-line use of metformin remained stable (91% of new prescriptions in 2017 vs. 91% 2010). Over the study period there was little change in average glycaemic response and treatment discontinuation. There was a modest reduction in weight second and third-line (second line 2017 vs. 2010: -1.5 kg (95%CI -1.9;-1.1), $p<0.001$), and a slight reduction in systolic blood pressure first to third-line (2017 vs. 2010 difference range -1.7 to -2.1 mmHg, all $p<0.001$). Hypoglycaemia rates

decreased second-line (incidence rate ratio 0.94 per-year (95%CI 0.88;1.00, p=0.04)), mirroring the decline in use of sulfonylureas.

Conclusions

Recent changes in prescribing of therapy in type 2 diabetes have not led to a change in glycaemic response and have resulted in modest improvements in other population-level short-term clinical outcomes.

Introduction

Prescribing of glucose-lowering therapies for people with type 2 diabetes has changed markedly in recent years. International guidelines have been updated to include a much greater choice of agents when additional therapies after metformin are required to achieve glycaemic control.(1-4) Newer drug classes including DPP4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists are now established alongside the longstanding options sulfonylureas, thiazolidinediones and insulin. Choice between these agents is left largely to the clinician and patient. Recent studies show that there have been marked changes in which agents are initiated after metformin, with a declining use of sulfonylureas and increasing and earlier use of DPP4 inhibitors and SGLT2 inhibitors in both the US, Europe and UK.(5-8)

Although studies have suggested the glucose-lowering effectiveness of agents typically added to metformin may be comparable,(1, 9, 10) there are well established differences between the different drug classes in weight change and side-effects. GLP-1 receptor agonists and SGLT2 inhibitors are associated with weight loss whereas DPP4 inhibitors are weight neutral and sulfonylureas can promote weight gain.(9, 10) Hypoglycaemia risk is greater with sulfonylureas and insulin relative to other agents.(9) Despite these known differences in non-glycaemic effects between agents, evidence of the impact of recent changes in prescribing on population-level clinical outcomes is limited.(5, 7, 11, 12) In this study we aimed to describe changes in prescribing of glucose-lowering drugs for people initiating first to fourth line therapy between 2010 and 2017 in the UK, a setting where prescribing does not reflect the ability of people to pay. We further examined population-level time trends in the short-term

clinical outcomes of glycaemic response, weight change, blood pressure change, hypoglycaemia, and treatment discontinuation.

Materials and methods

Data source and data extraction

We conducted a population-based analysis of anonymized primary care data from the UK's Clinical Practice Research Database (CPRD). CPRD is a population representative database containing demographic, clinical and prescription primary care records of individuals.(13) Although CPRD includes full prescription records no data on drug dispensation are available. CPRD has been extensively used to study drug prescribing and clinical outcomes in type 2 diabetes.(14) We analysed data from the January 2018 release of CPRD, including all practices that were still contributing to CPRD in 2017 to ensure that changes in prescribing did not reflect changes in the practices captured in CPRD over the study period. We classified glucose-lowering drugs into drug classes according the British National Formulary sections 6.1.1 and 6.1.2.(15) Drugs were categorised as metformin, sulfonylureas, thiazolidinediones, DPP4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, insulin or Other (Meglitinides and alpha-glucosidase inhibitors, which are prescribed very rarely in the UK). Scientific approval was granted by the CPRD Independent Scientific Advisory Committee (ISAC 13_177RA4R).

Study population

We extracted the clinical and prescription records of all people with type 2 diabetes who started at least one glucose-lowering drug for the first time ever between 1st January 2010 and 31st December 2017 and met CPRD quality assurance criteria (n=78,857). Inclusion criteria and data ascertainment

followed our previously reported CPRD cohort profile.(16) Type 2 diabetes was defined largely on the basis of prescriptions for non-insulin diabetes therapies rather than diagnostic medical codes to minimize coding errors.(17) We excluded people with diagnostic codes for other forms of diabetes or polycystic ovary syndrome which can be treated with metformin. To remove people with type 1 diabetes, who may be miscoded as Type 2, we excluded peoples with an age at diagnosis <35 or on insulin treatment within 12 months of diagnosis. Consequently, people with type 2 diabetes whose first-line therapy was insulin were not included. We defined date of diabetes diagnosis as the earliest of: first prescription for a non-insulin diabetes therapy; first HbA_{1c} result >=6.5% (48 mmol/mol); or first diabetes diagnostic code.

Study design

The study exposure was a new first to fourth line drug prescription record for an individual within the study period. New drug prescriptions (and their corresponding start dates) were defined as the first ever prescription of a drug in a class for a individual. First, second, third or fourth-line prescription categories were defined based on the order of new drug prescriptions for individuals. Every time an individual started a new drug class we assigned this to the next line of therapy, regardless of whether their concomitant therapy changed at a similar time point.

The primary unit of analysis was line of therapy. This meant individuals who started more than one new therapy over the study period contributed to the analysis more than once at different lines of therapy (see Supplementary Flowchart).

Study outcomes

For each line of therapy, we evaluated annual time trends in the drug classes initiated, and time trends in changes in HbA_{1c}, weight, systolic and diastolic blood pressure, hypoglycaemia rates and treatment discontinuation after therapy start. To evaluate all outcomes we used a 'new user' design which mitigated immortal time bias.(18) Patients were followed up from their drug start date until there was any change in diabetes therapy or the end of the study period specific to each outcome. A change in therapy could be the addition of a new glucose-lowering drug or the stopping of the drug of interest or any concomitant glucose-lowering drug. Patients were considered to have stopped a drug if there was a subsequent gap in prescribing of that drug for at least 6 months.(16)

We defined glycaemic response (the change in HbA_{1c}), weight change and blood pressure change as the absolute change from baseline to 6 months (6 month measure minus baseline measure). For glycaemic response, baseline HbA_{1c} was defined as the closest HbA_{1c} to the drug start date in the 3 months prior to the drug start date. Individuals with missing baseline HbA_{1c} measures (9% of the cohort) were excluded from the complete case analysis of glycaemic response as the change from baseline in HbA_{1c} could not be calculated. HbA_{1c} at 6 months was defined as the closest HbA_{1c} to 6 months after the drug start date (+/-3 months). Glycaemic response was only valid if there were no changes in glucose-lowering therapy between 2 months prior to the baseline HbA_{1c} and the date of the 6 month HbA_{1c}. The same approach was used for weight change and blood pressure change.

We defined hypoglycaemia as the first Read code for hypoglycaemia up to 2 years after starting a line of therapy, using a previously published Read code list for hypoglycaemia.(19) Due to the low number of hypoglycaemia events captured in primary care we grouped data into biannual categories representing four distinct periods (2010-11, 2012-13, 2014-15, 2016-17).

We examined treatment discontinuation by estimating the proportion of people who stopped a therapy within 3 months, 6 months and 1 year. 6 months follow-up after discontinuation was required to determine no new prescriptions were issued.

Statistical analysis

We examined annual time trends for each clinical outcome and each line of therapy in separate analysis. We described trends in baseline clinical characteristics as mean (standard deviation) per calendar year. All outcomes analyses were standardized to the mean baseline values of relevant measures for individuals starting that line of therapy in 2017.

To evaluate changes in relative prescribing for each line of therapy we calculated the proportion of new prescriptions for each drug class in each calendar year as the:

$$\frac{total\ number\ of\ new\ prescriptions\ of\ the\ drug}{total\ number\ of\ new\ prescriptions}$$

When describing first-line therapy all drugs except metformin and sulfonylureas were pooled. Within drug class trends for DPP4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors and sulfonylureas (2014-2017) were estimated using the same approach.

We evaluated non-linear time trends in glycaemic response, weight change and blood pressure change for each calendar year using linear regression with calendar year as a categorical covariate and adjustment for baseline HbA_{1c}, age at therapy, duration of diabetes, and the baseline measure of the outcome for non-glycaemic outcomes. We used complete case analysis including people only if they had both a valid baseline measure and a valid 6 month measure. To assess the potential influence of missing data we compared the characteristics of individuals with missing data with those included in the analysis. Multiple imputation was not conducted as it is only valid under the missing at random assumption, meaning the differences between the observed and missing data could can be explained by other recorded measures. However, we felt outcome data were likely to depend on their actual value (missing not at random), which will be the case if, for example, individuals with poorest glycaemic control are also those most likely to miss a follow-up clinical appointment to have their HbA1c measured. Hypoglycaemia biannual time trends were estimated as rates per 1,000 person-years using Poisson regression, adjusted for age, duration, and baseline HbA_{1c}.

Summary measures for each outcome (including baseline HbA_{1c}) were calculated as follows; 1) the 2017 vs. 2010 marginal contrast from the multivariable linear regression models described above;(20) 2) the linear time trend, as the beta coefficient from a multivariable linear regression treating calendar year as a continuous rather than categorical covariate.

To evaluate changes in treatment discontinuation we calculated the proportion of new prescriptions that were stopped within 3 months, 6 months and 1 year for each line of therapy for each calendar year as:

$$\frac{total\ number\ of\ new\ prescriptions\ stopped\ within\ time\ period}{total\ number\ of\ new\ prescriptions}$$

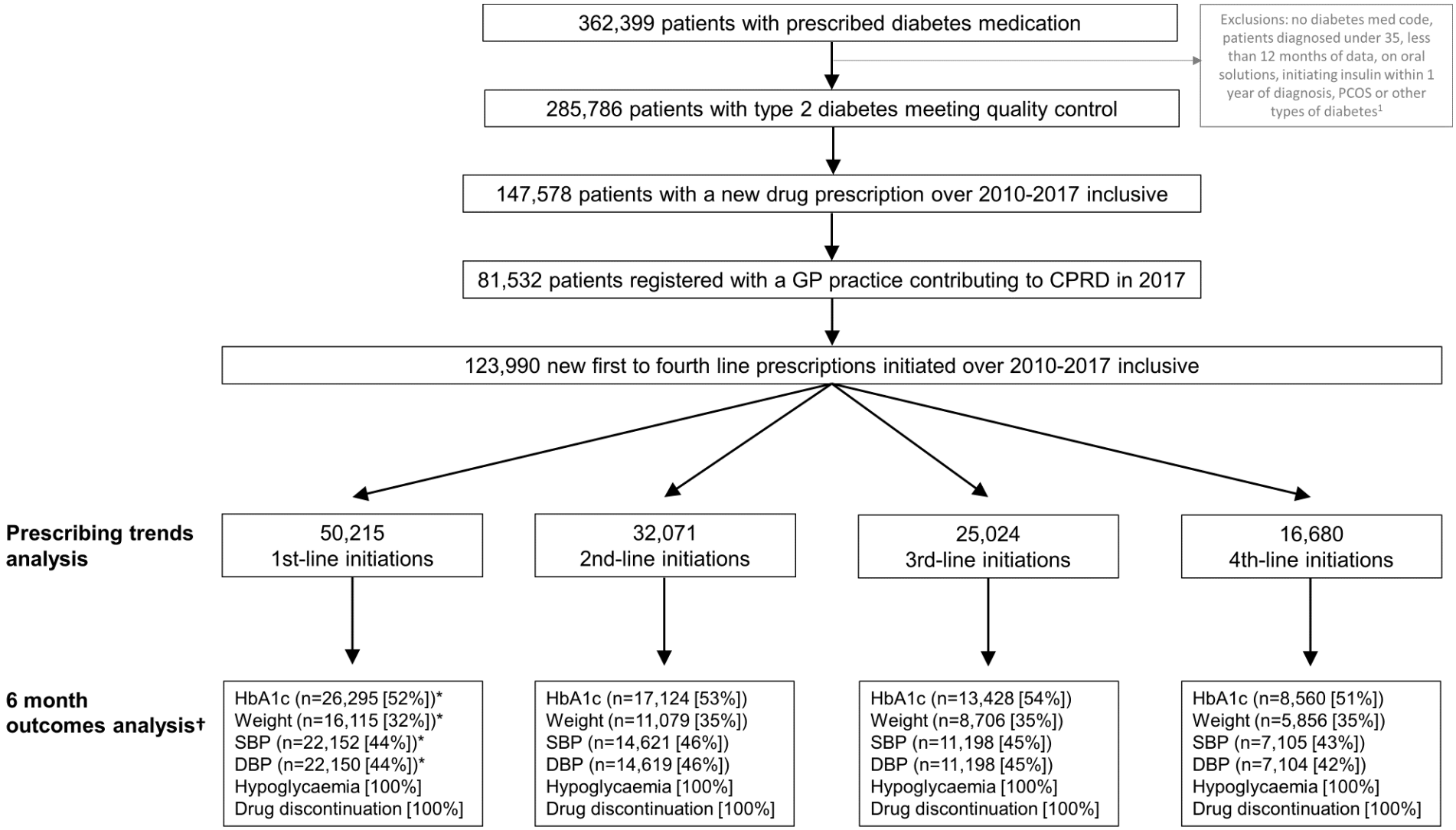
For an overview of the flowchart for the study and outcomes evaluated please see Figure 1.

All data extraction and analysis was conducted in Stata v14.0.

Sensitivity analysis

We repeated all outcomes analysis using change in each measure from baseline to 12 months as the outcome in a distinct cohort of people with 12 month measures of each outcome (closest +/-3 months as for the definition of 6 month change). Participants commencing therapy in 2017 were not included in this analysis as 12 months of follow-up had not accrued. We also evaluated the sensitivity of results to our definition of line of therapy by repeating all second-line analyses in a subset of people who were initiated on metformin first-line and then added a different therapy to metformin (rather than stopping metformin). To assess whether changes in outcomes over time were likely to be due to changes in the drugs prescribed we compared time trends in weight change and hypoglycaemia using the same models described above, with drug as an additional covariate.

Figure 1: Overview of study design, and patients included in each analysis



†Individuals on unchanged therapy, ensuring no overlap between lines of therapy.
*N [%] with valid data for 6 month analysis. Each outcome was defined the closest available measure to 6 months after therapy initiation +/- 3 months
[1] Rodgers LR, Weedon MN, Henley WE, Hattersley AT, Shields BM. Cohort profile for the MASTERMIND study: using the Clinical Practice Research Datalink (CPRD) to investigate stratification of response to treatment in patients with type 2 diabetes. BMJ open. 2017;7(10):e017989

Results

123,990 new first to fourth line prescriptions from 81,532 individuals were eligible for inclusion. 40% (50,215) were for a first-line prescription, 26% (32,071) were second-line, 20% (25,024) were third-line and 13% (16,680) were fourth-line (Figure 1). The baseline clinical characteristics of people starting each line of therapy in 2017 are shown in Supplementary Table 1. Average baseline HbA_{1c} increased second to fourth-line over the study period; average baseline weight increased first-line but there was little difference for other lines of therapy. The proportion of people with valid data for analysis of each outcome is shown in the Supplementary Flowchart.

Changing prescribing of glucose lowering therapy

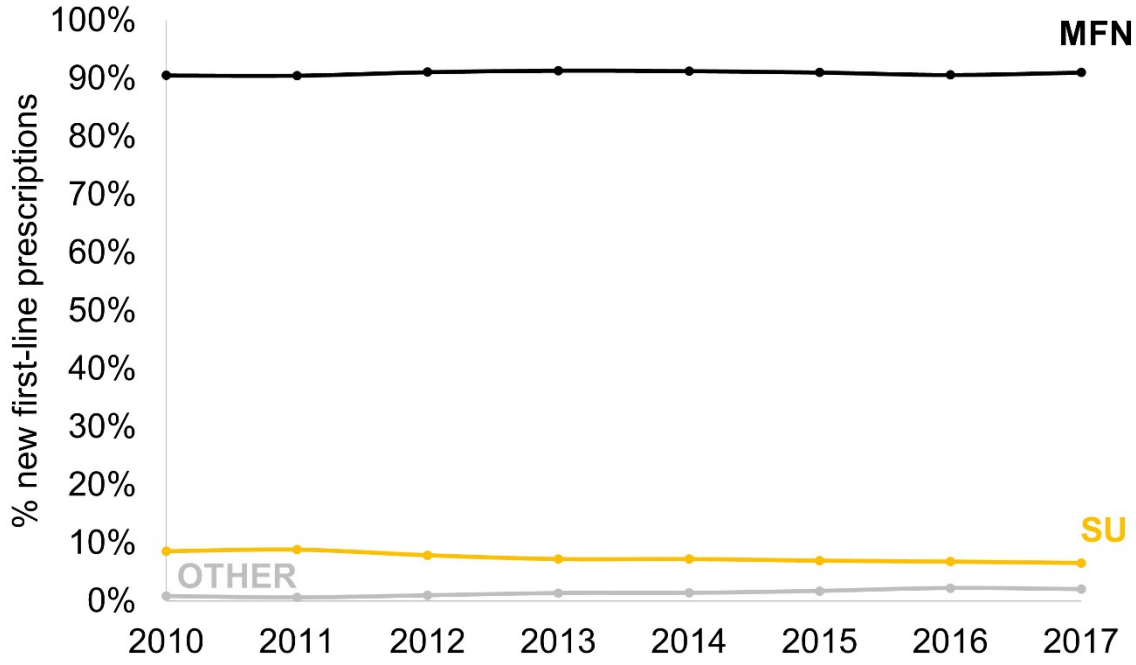
We found marked changes in relative prescribing of second to fourth-line therapy (Figure 2). DPP4 inhibitors were by 2017 the most commonly initiated second-line therapy (2017 41% of new second-line; 2010 22% of new second-line), whilst second-line prescribing of sulfonylureas decreased (2017 29%; 2010 53%). SGLT2 inhibitors were the most common fourth-line therapy in 2017 (40% prescriptions) and their use second-line (19% of new 2017 prescriptions) and third-line (28% of new 2017 prescriptions) increased rapidly following their introduction in 2013. Fourth-line prescribing of injectable therapy decreased (GLP-1 receptor agonists: 2017 11%, 2010 20%; insulin: 2017 17%, 2010 21%), and remained low second and third-line. First-line use of metformin remained stable (2017 91%; 2010 91%).

Evaluating new first to fourth line drug initiations as a whole (Supplementary Figure 2), we found SGLT2 inhibitors (17% of total new prescriptions in 2017) were more commonly initiated in 2017 than sulfonylureas (14% in 2017). New

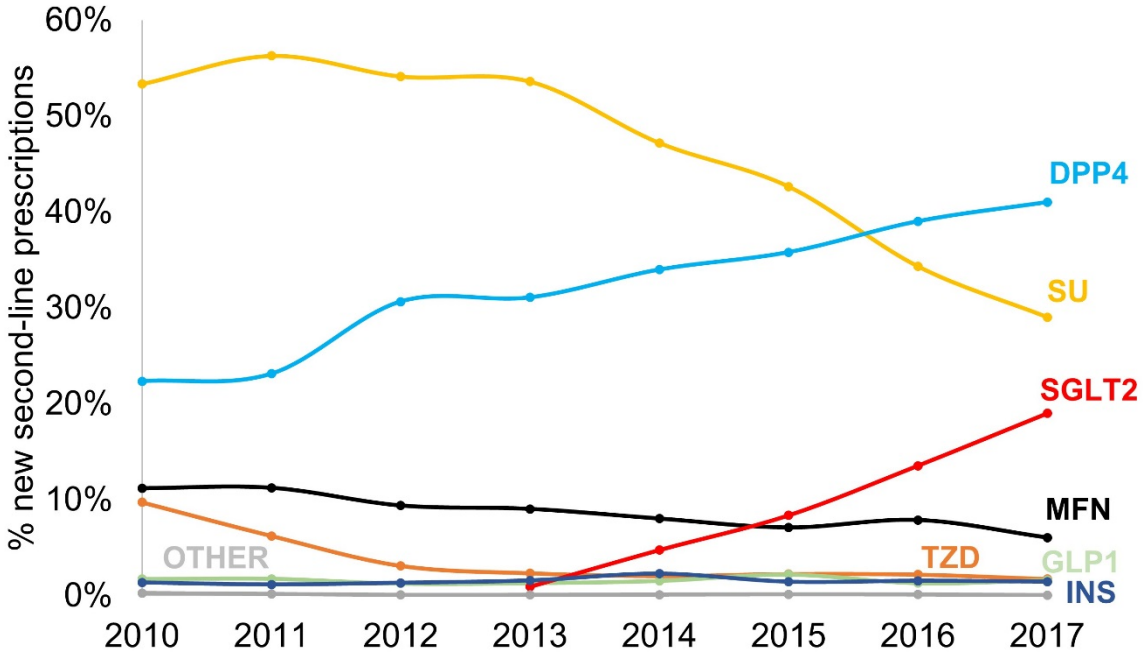
prescribing of insulin (2017 5%; 2010 5%) and GLP-1 receptor agonists (range 4% to 3%) remained constant over the study period.

Figure 2: Time trends in new drug prescriptions for a) first-line b) second-line c) third-line d) fourth-line therapy. The prescriptions for each drug class each year are given as a percentage of total new drug prescriptions for that year.

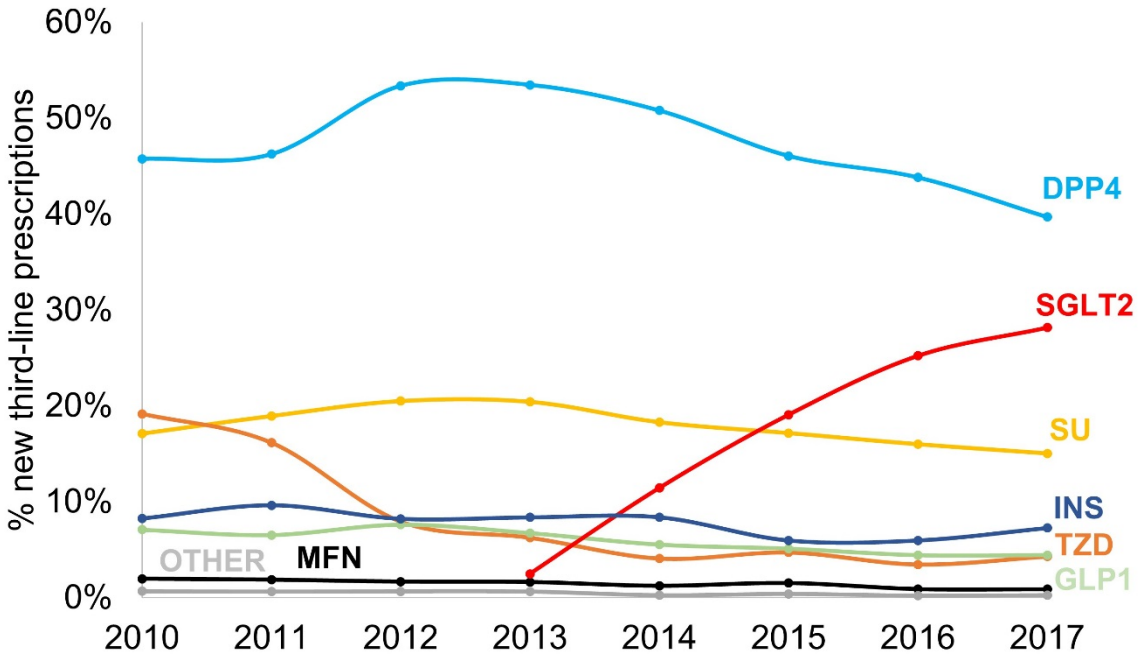
a) first-line



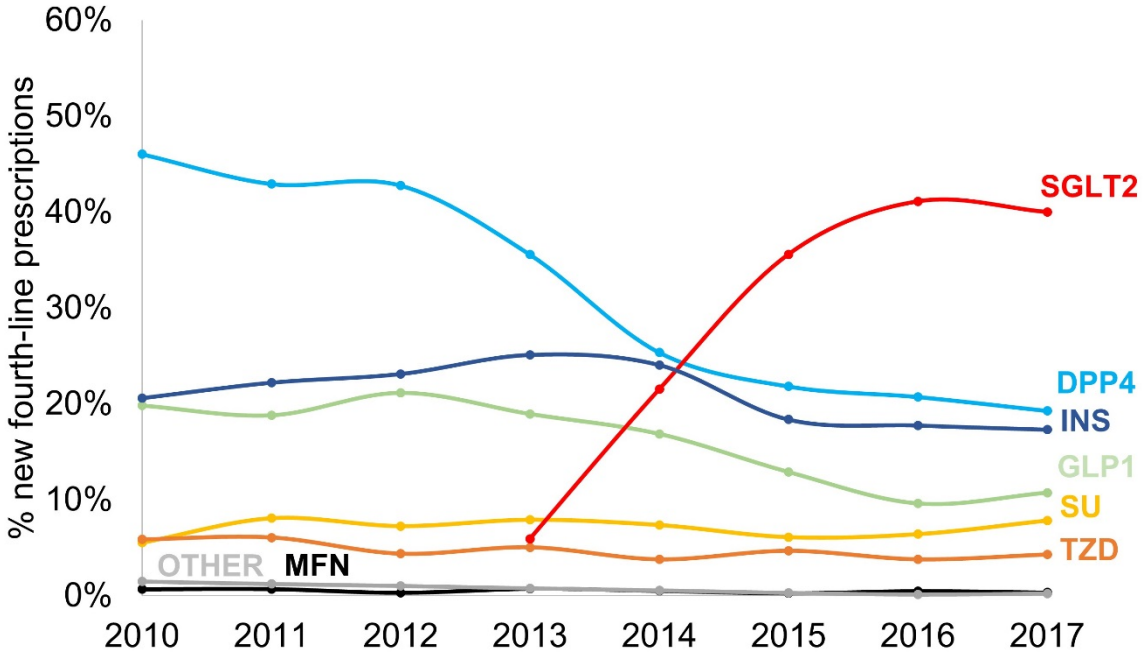
b) second-line



c) third-line



d) fourth-line



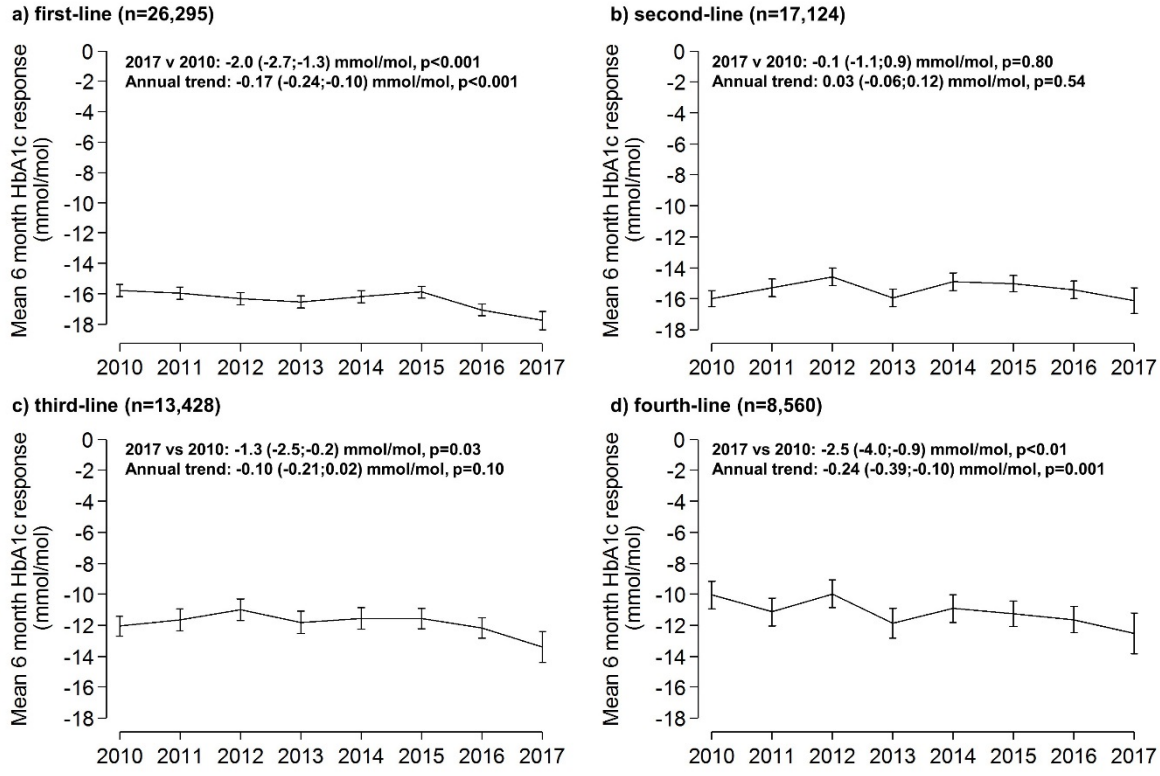
Changes in within class prescribing

In addition to changes in class of agent there have been marked recent changes in prescription of individual agents within a class. Over 2014 to 2017 for DPP4 inhibitors, there was decreasing use of sitagliptin (2017 37%; 2014 56%), but increasing use of alogliptin (2017 25%; 2014 1%) and linagliptin (2017 31%; 2014 25%) (Supplementary Figure 2a). For GLP-1 receptor agonists use of once-weekly dulaglutide increased to 51% of the class total following its introduction in 2015. For SGLT-2 inhibitors there was increasing use of empagliflozin (2017 46%; 2015 8%) but decreasing use of dapagliflozin (2017 41%; 2014 92%) (Supplementary Figure 2c). Gliclazide use has remained stable (2017 91% of all sulfonylureas; 2010 89%) (Supplementary Figure 2d).

Reduction in HbA1c

Average reductions in HbA_{1c} at 6 months were relatively constant over 2010 to 2017 across all lines of therapy (Figure 3). There was no evidence of a change in glycaemic response for second-line therapy (2017 *vs.* 2010 change 0.0% (-0.1 mmol/mol), p=0.80). For first, third, and fourth-line therapy there was evidence of a statistically significant trend towards improved glycaemic response, although this translated to a modest absolute improvement in reduction in HbA_{1c} (2017 *vs.* 2010 change range 0.2-0.3% (1.3 to 2.5 mmol/mol), all p<0.05).

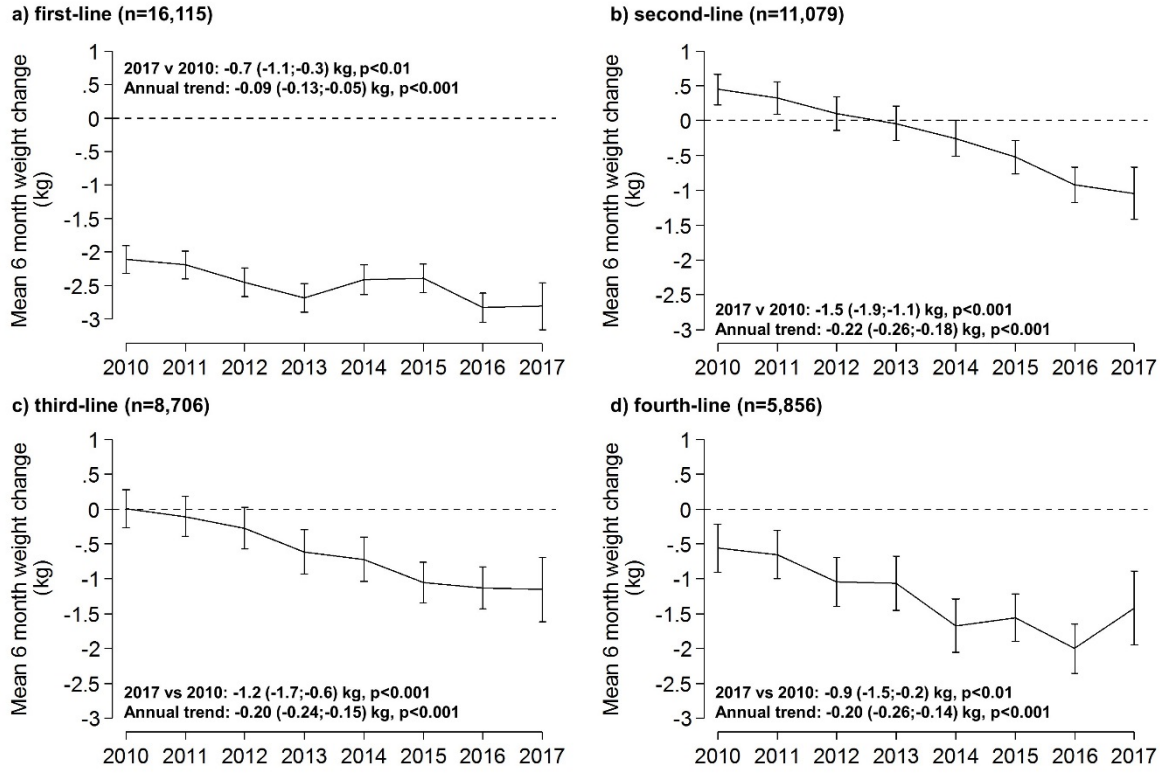
Figure 3: Mean HbA_{1c} response at 6 months, 2010-2017 for a) first-line b) second-line c) third-line d) fourth-line. Error bars are 95% confidence intervals. Data are standardised to the average baseline HbA_{1c}, age at diagnosis and duration of diabetes, specific to each drug line in 2017.



Weight change

Although there was a trend towards greater weight loss at 6 months for all lines of therapy, this was most marked second and third-line (2017 *vs.* 2010 second-line -1.5kg and third-line -1.2kg, both p<0.001; overall time trends for improvement in weight change p<0.001 for all lines of therapy) (Figure 4). Patients starting second-line therapy on average lost rather than gained weight when comparing 2017 with 2010.

Figure 4: Mean change in weight at 6 months, 2010-2017 for a) first-line b) second-line c) third-line d) fourth-line. Error bars are 95% confidence intervals. Data are standardized to the average baseline weight, baseline HbA_{1c}, age at diagnosis and duration of diabetes, specific to each drug line in 2017.



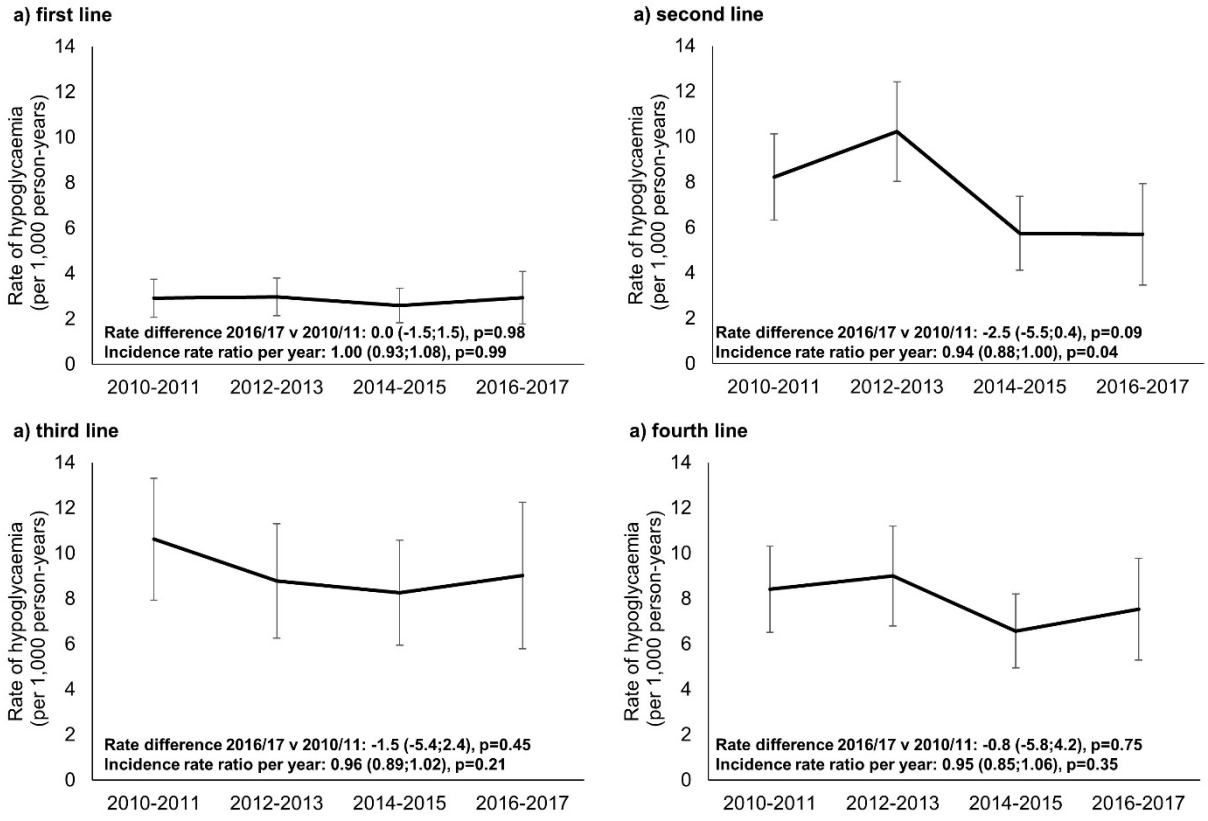
Blood pressure

We found a trend towards a modest improvement in systolic blood pressure at 6 months for all lines of therapy (2017 *vs.* 2010 range -1.7 to -2.1 mmHg, all p<0.001, Supplementary Figure 3a). There was no change in diastolic blood pressure (Supplementary Figure 3b).

Hypoglycaemia

We observed a decrease in hypoglycaemia rates for people starting second-line therapy (2017 rate 5.7 (95% CI 3.5; 7.9) per 1,000 person-years; 2010 rate 8.2 (95% CI 6.3; 10.1) per 1,000 person-years (Figure 5, Supplementary Table 2).

Figure 5: Hypoglycaemia rates per 1,000 person-years by 2 year period for a) first-line b) second-line c) third-line d) fourth-line therapy. Rates represent the occurrence of hypoglycaemia over the first two years after starting a line of therapy.



Treatment discontinuation

Treatment discontinuation at 3 months, 6 months and 1 year after initiating therapy was stable over 2010-2017 (Supplementary Table 3). The proportion of people discontinuing within 3 months in 2017 compared to 2010 was as follows: first-line 4% vs 3%; second-line 7% vs 9%; third-line 12% vs 9%; fourth-line 10% vs 9%.

Sensitivity analysis

Baseline characteristics of people excluded as they did not have valid clinical measures were similar to those included in analysis (Supplementary Table 4). Time trends for outcomes at 12 months were similar to at 6 months for glycaemic response (Supplementary Figure 4), weight change (Supplementary Figure 5), and blood pressure (Supplementary Figure 6). Second-line prescribing trends and clinical outcomes in the subset of people adding a second-line drug to continued first-line metformin therapy (73% of people included in the primary analysis) were near identical to the primary analysis (Supplementary Figure 7). Differences in weight change trends became minimal when models were adjusted for drug therapy as a covariate (Supplementary Table 5a), and after adjustment for drug there was no evidence of a difference in risk of hypoglycaemia over time (Supplementary Table 5b).

Discussion

Our study describes, for the first time, recent population-level time trends in clinical outcomes after initiating glucose-lowering therapy over 2010 to 2017, a period where there was drastic changes in type 2 diabetes prescribing patterns. There were modest population-level improvements in weight change and rates of hypoglycaemia for people starting additional therapy after metformin, but little

change in glycaemic response, blood pressure change or treatment discontinuation. Data on these important short-term clinical outcomes provide timely context to the worldwide trend towards prescribing of newer more costly glucose-lowering agents. We also provide updated information on UK prescribing trends: 1) increased and earlier initiation of DPP4 inhibitors; 2) reduced initiation of sulfonylureas second-line; 3) a rapid increase in initiation of SGLT2 inhibitors; and 4) decreased initiation of injectable therapy (GLP-1 receptor agonists and insulin).

Whilst our retrospective analysis precludes causal inference and can only show temporal correlation, the time trends in outcomes reflect the known effects of the different drug classes on clinical outcomes. As might be expected from previous comparative analysis,(9, 10) there was an improvement in weight change and reduction in rates of hypoglycaemia where there was a rapid increase in the use of SGLT2 inhibitors and DPP4 inhibitors in place of sulfonylureas. These changes were attenuated by adjustment for drug, supporting the suggestion that the population-level improvements relate to changes in prescribing. Although recent meta-analyses have found little difference in glycaemic response when comparing therapies added to metformin,(1, 9) some studies have reported increased response with sulfonylureas compared with other agents,(21-23) or lower response with DPP4 inhibitors,(24) and so it is reassuring that we found second-line glycaemic response was stable despite the shift in prescribing. Newer agents, in particular SGLT2 inhibitors, have been associated with modestly lower blood pressure.(25-28) However whilst there were small improvements over time in blood pressure change with second to fourth-line therapy there were also

improvements first-line where prescribing was unaltered. This suggests that improvements do not solely reflect prescribing changes.

The trends in new prescribing in this study are consistent with previous studies of UK primary care data,(7) including a recent analysis which documented extensive geographical variation in UK prescribing.(6) Comparison with US data suggest newer therapies have been adopted more quickly in the UK than in the US; in the US sulfonylureas remain the most common second-line therapy.(5) However, trends in new prescribing are similar in the US, with decreasing second-line use of sulfonylureas (46% of new second-line prescribing in 2016 compared to 55% in 2010) and increasing use of DPP4 inhibitors (20% in 2016; 14% in 2010). The increased cost of newer agents may explain their relatively slower uptake in the US.(5)

There are limited recent studies in time trends of clinical outcomes. A recent analysis of 1.7 million individuals with US Medicare found no overall change in glycaemic control or rates of hypoglycaemia over 2006 to 2013, but unlike our study did not study people initiating new therapy.(12) Although overall hospital admission rates for hypoglycaemia in England were stable from 2010 to 2014,(29) a different study observed declining overall rates of hypoglycaemia requiring hospitalization in UK patients over, but not under, 65 from 2009 to 2013 in the context of declining use of sulfonylureas in this older age group,(30) The changes observed in these studies examining the overall population of people with type 2 diabetes will lag considerably behind those observed in our analysis of new therapy initiation, as once initiated a glucose lowering therapy may be continued for decades.

Strengths of the study include our approach examining new prescribing, which allowed interrogation of time trends whilst accounting for the increasing

prevalence of type 2 diabetes, which in the UK is due more recently to declining mortality rather than increasing incidence,(31, 32) and means prescribing of glucose-lowering therapy is increasing in absolute terms.(6, 33) Our definition of type 2 diabetes should minimize misclassification.(16) Our study provides a near complete picture of UK prescribing, as in the UK type 2 diabetes is largely managed in primary care. Even new therapy initiated on the advice of a specialist will usually be prescribed by the patients' primary care physician. A limitation of this study is the weakness in the way hypoglycaemia is recorded. It is likely that many episodes of hypoglycaemia will be missing from an individuals' primary care record, as mild hypoglycaemia or more severe hypoglycaemia requiring attendance in secondary care are poorly recorded. However, previous studies have provided useful insight into hypoglycaemia using similar definitions in the same dataset.(34) Although the missing records mean the absolute rates of hypoglycaemia in this study will be an underestimate, the specificity of our key finding, a relative decrease in hypoglycaemia rates second-line where use of sulfonylureas has markedly declined, is reassuring. A further limitation is the complete case analysis used, as there were a significant amount of missing data for each of the clinical outcomes evaluated (Figure 1). A complete case analysis has however been used in other recent descriptive studies evaluating the comparative effectiveness of diabetes therapies in primary care data.(24, 35) In our opinion multiple imputation would not be appropriate in this dataset as the missing at random assumption required for this analysis is very unlikely to be met – for example an individuals' glycaemic control may influence their likelihood of repeat HbA1c testing, and so likelihood of study inclusion. We used sensitivity analysis rather than multiple imputation to check the robustness of our findings,

demonstrating consistent findings for both 6 and 12 month clinical outcomes, with each analysis including distinct cohorts of individuals. Whilst our study provides timely information on population-level trends, further observational studies, building on recent work, will be needed to establish the real-world comparative effectiveness of individual drug classes at different lines of therapy.(10, 35)

Our results show that prescribing of glucose lowering therapy in Type 2 diabetes is rapidly changing towards newer, more expensive agents. Changes in prescribing appear to have pre-empted rather than reflected changes to clinical guidelines.(1) In particular second-line prescribing of DPP4 inhibitors increased rapidly long before treatment guidelines were updated to position them along sulfonylureas and pioglitazone as second-line options.(36) The positive trends in weight change, hypoglycaemia and blood pressure are likely to have improved the quality of life for patients, and a reduction in hypoglycaemia is also likely to have a cost benefit.(37) However, given the much higher cost of newer drug options, the modest improvement we observed in clinical outcomes suggests further studies are needed to evaluate cost-effectiveness of the newer glucose-lowering agents. Recent evidence suggests there may be potential for a more stratified approach to prescribing of type 2 diabetes therapy, meaning prescribing decisions can be better informed through identification of individuals or subgroups who differ in their likely glycaemic response or risk of side-effects with individual agents.(38-40)

We did not evaluate microvascular or macrovascular outcomes in this study, but a cardiovascular benefit in select participants with established cardiovascular disease or at high risk, has recently been demonstrated in individual trials for the SGLT2 inhibitors empagliflozin and canagliflozin, and GLP-1 receptor

agonist liraglutide.(25, 41, 42) A recent meta-analysis of randomized trials suggested that in contrast to SGLT2 inhibitors and GLP-1 receptor agonists there is no short term mortality benefit with DPP4 inhibitors.(43) Given the recent changes in treatment guidelines to consider cardiovascular risk when choosing therapy,(4) and the fact all three classes have now been prescribed in significant numbers for some years, an evaluation of longer-term trends in microvascular and macrovascular complications would be of considerable interest.

Conclusions

The trend towards prescribing of newer, more expensive, glucose-lowering medication in the UK has coincided, for people initiating new therapy, with a likely reduction in hypoglycaemia rates and a modest improvement in weight and blood pressure, but little change in glycaemic response or treatment discontinuation. These results demonstrate the potential population-level impact of the rapid changes which are occurring in prescribing of glucose-lowering therapy worldwide.

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Supplementary Material

Supplementary table 1: Average baseline clinical characteristics by calendar year and therapy (2010-2017)

a) first-line

	2010	2011	2012	2013	2014	2015	2016	2017
N	6682	6252	6170	6341	5993	6719	6709	5349
Baseline HbA_{1c} (mmol/mol)	71 (22)	72 (22)	73 (22)	72 (22)	71 (22)	72 (23)	72 (22)	71 (22)
Age at therapy (years)	62 (12)	62 (12)	62 (12)	62 (12)	62 (12)	62 (12)	62 (12)	62 (12)
Duration of diabetes (years)	2 (3)	2 (3)	2 (3)	2 (3)	2 (3)	2 (3)	2 (3)	2 (3)
Sex (% Male)	59%	59%	59%	58%	58%	58%	58%	59%
Ethnicity (% White/missing)	94%	93%	94%	93%	92%	93%	92%	92%
BMI (kg/m^2)	33 (7)	33 (7)	33 (7)	33 (7)	33 (7)	33 (7)	33 (7)	33 (7)
Weight (kg)	93 (21)	93 (21)	94 (21)	94 (22)	94 (22)	95 (22)	95 (22)	96 (22)
eGFR (mL/min/1.73 m^2)	80 (19)	81 (19)	82 (19)	83 (19)	83 (19)	83 (19)	83 (19)	83 (18)
Systolic blood pressure (mmHG)	137 (16)	136 (16)	136 (16)	136 (16)	135 (15)	136 (16)	136 (16)	135 (16)
Diastolic blood pressure (mmHG)	80 (10)	80 (10)	80 (10)	79 (10)	79 (10)	79 (10)	79 (10)	80 (10)
HDL (mmol/L)	2.8 (1)	2.8 (1.1)	2.9 (1)	2.8 (1.1)	2.8 (1)	3 (1.2)	3.3 (1.3)	3.3 (1.3)
LDL (mmol/L)	1.2 (0.4)	1.2 (0.4)	1.2 (0.3)	1.2 (0.4)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
Triglycerides (mmol/L)	2.5 (2.2)	2.5 (2.2)	2.4 (2.2)	2.5 (2.3)	2.5 (2.3)	2.5 (2)	2.5 (2.3)	2.5 (1.9)

b) second-line

	2010	2011	2012	2013	2014	2015	2016	2017
N	4387	3960	3875	3792	3745	4276	4258	3778
Baseline HbA_{1c} (mmol/mol)	72 (19)	74 (20)	75 (20)	76 (20)	76 (19)	76 (20)	75 (20)	75 (20)
Age at therapy (years)	63 (12)	63 (12)	63 (12)	63 (13)	63 (12)	63 (12)	63 (12)	63 (12)
Duration of diabetes (years)	5 (4)	5 (4)	5 (4)	5 (4)	5 (4)	5 (4)	6 (5)	6 (5)
Sex (% Male)	60%	59%	59%	60%	58%	59%	58%	60%
Ethnicity (% White/missing)	94%	94%	94%	93%	93%	94%	93%	93%
BMI (kg/m^2)	32 (7)	32 (7)	32 (7)	32 (7)	33 (7)	33 (7)	33 (7)	33 (7)
Weight (kg)	93 (22)	93 (22)	92 (21)	92 (22)	93 (22)	94 (22)	94 (22)	94 (21)
eGFR (mL/min/1.73 m^2)	80 (21)	81 (21)	80 (21)	81 (21)	81 (21)	82 (21)	82 (21)	81 (21)
Systolic blood pressure (mmHG)	135 (16)	134 (15)	134 (15)	134 (15)	133 (14)	133 (14)	134 (14)	134 (15)
Diastolic blood pressure (mmHG)	78 (10)	78 (10)	78 (10)	78 (10)	77 (9)	77 (9)	78 (9)	78 (9)
HDL (mmol/L)	2.3 (0.9)	2.4 (0.9)	2.4 (1)	2.4 (1)	2.4 (1)	2.6 (1.1)	2.8 (1.1)	2.9 (1.2)
LDL (mmol/L)	1.2 (0.4)	1.2 (0.4)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
Triglycerides (mmol/L)	2.3 (1.9)	2.5 (2.3)	2.4 (2.2)	2.4 (1.9)	2.5 (2.2)	2.5 (2)	2.4 (1.8)	2.5 (2.1)

c) third-line

	2010	2011	2012	2013	2014	2015	2016	2017
N	3455	3045	2871	2701	2912	3413	3462	3165
Baseline HbA_{1c} (mmol/mol)	73 (18)	76 (18)	76 (18)	77 (19)	77 (19)	78 (18)	77 (19)	77 (19)
Age at therapy (years)	63 (11)	64 (12)	64 (12)	64 (12)	65 (12)	64 (12)	64 (12)	64 (12)
Duration of diabetes (years)	8 (5)	8 (5)	8 (5)	8 (5)	8 (5)	8 (5)	8 (5)	9 (5)
Sex (% Male)	60%	59%	58%	59%	59%	59%	59%	58%
Ethnicity (% White/missing)	94%	94%	94%	93%	94%	94%	93%	92%

BMI (kg/m²)	33 (7)	33 (7)	33 (7)	33 (7)	33 (7)	33 (7)	33 (7)	33 (7)
Weight (kg)	94 (21)	94 (22)	95 (23)	93 (22)	93 (22)	94 (21)	95 (22)	93 (21)
eGFR (mL/min/1.73 m²)	79 (21)	78 (22)	78 (23)	77 (23)	77 (23)	79 (22)	79 (22)	78 (23)
Systolic blood pressure (mmHG)	135 (16)	135 (16)	135 (16)	134 (15)	133 (15)	133 (15)	133 (14)	134 (15)
Diastolic blood pressure (mmHG)	77 (10)	77 (10)	77 (9)	77 (9)	76 (9)	77 (9)	77 (9)	77 (9)
HDL (mmol/L)	2.2 (0.8)	2.2 (0.9)	2.2 (0.9)	2.2 (0.9)	2.2 (0.9)	2.4 (1)	2.8 (1.1)	2.7 (1.2)
LDL (mmol/L)	1.2 (0.4)	1.2 (0.4)	1.1 (0.3)	1.1 (0.3)	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)
Triglycerides (mmol/L)	2.2 (1.8)	2.3 (1.8)	2.3 (1.7)	2.3 (1.6)	2.3 (1.8)	2.3 (1.6)	2.5 (2)	2.4 (1.6)

d) fourth-line

	2010	2011	2012	2013	2014	2015	2016	2017
N	2083	2031	1943	1805	1980	2374	2321	2143
Baseline HbA_{1c} (mmol/mol)	76 (19)	78 (19)	79 (19)	81 (20)	81 (19)	81 (19)	81 (19)	80 (18)
Age at therapy (years)	63 (11)	64 (10)	64 (11)	64 (11)	64 (11)	65 (11)	64 (11)	64 (11)
Duration of diabetes (years)	10 (5)	10 (5)	10 (5)	10 (6)	10 (6)	11 (6)	11 (6)	11 (6)
Sex (% Male)	59%	58%	58%	57%	58%	59%	59%	59%
Ethnicity (% White/missing)	94%	94%	95%	93%	94%	95%	93%	92%
BMI (kg/m²)	34 (7)	34 (7)	33 (7)	33 (7)	33 (7)	33 (7)	33 (7)	33 (7)
Weight (kg)	95 (22)	96 (22)	96 (22)	95 (22)	96 (21)	95 (22)	94 (21)	94 (21)
eGFR (mL/min/1.73 m²)	77 (21)	77 (21)	76 (23)	77 (23)	76 (24)	78 (22)	78 (23)	77 (23)
Systolic blood pressure (mmHG)	135 (15)	135 (15)	135 (16)	134 (15)	133 (15)	133 (15)	133 (14)	133 (14)
Diastolic blood pressure (mmHG)	77 (9)	77 (9)	76 (10)	76 (10)	76 (10)	76 (9)	76 (9)	77 (9)
HDL (mmol/L)	2.2 (0.8)	2.2 (0.8)	2.2 (0.9)	2.1 (0.8)	2.1 (0.9)	2.3 (1)	2.6 (1)	2.7 (1.1)
LDL (mmol/L)	1.1 (0.4)	1.2 (0.4)	1.1 (0.3)	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)
Triglycerides (mmol/L)	2.3 (2.3)	2.2 (1.6)	2.2 (1.8)	2.2 (1.6)	2.3 (1.8)	2.3 (1.5)	2.4 (2.1)	2.4 (1.7)

Supplementary Table 2: Time trends in hypoglycemia rates for a) first-line b) second-line c) third-line d) fourth-line therapy.

a) first-line

	Person-time at risk	Number of events	Rate (per 1000 person-years)	95% Confidence intervals
2010-2011	15453	48	2.91	2.08;3.75
2012-2013	15953	51	2.98	2.14;3.81
2014-2015	16631	46	2.60	1.83;3.36
2016-2017	7903	25	2.93	1.77;4.10

b) second-line

	Person-time at risk	Number of events	Rate (per 1000 person-years)	95% Confidence intervals
2010-2011	9198	74	8.22	6.32;10.13
2012-2013	8297	84	10.23	8.03;12.42
2014-2015	8396	48	5.75	4.12;7.38
2016-2017	4373	25	5.70	3.46;7.94

c) third-line

	Person-time at risk	Number of events	Rate (per 1000 person-years)	95% Confidence intervals
2010-2011	6116	63	10.62	7.94;13.31
2012-2013	5457	47	8.78	6.26;11.30
2014-2015	5974	49	8.26	5.95;10.58
2016-2017	3348	30	9.01	5.79;12.24

d) fourth-line

	Person-time at risk	Number of events	Rate (per 1000 person-years)	95% Confidence intervals
2010-2011	2637	22	8.41	4.76;12.07
2012-2013	2405	22	9.00	5.18;12.82
2014-2015	2909	19	6.57	3.60;9.55
2016-2017	1726	13	7.53	3.42;11.65

Supplementary Table 3: Percentage of patients discontinuing a new drug a) within 3 months b) within 6 months c) within 12 months, by calendar year and line of therapy

a) within 3 months

	2010	2011	2012	2013	2014	2015	2016	2017
First line	3%	3%	3%	3%	3%	3%	3%	4%
Second line	9%	8%	9%	8%	9%	8%	9%	7%
Third line	9%	9%	8%	9%	10%	9%	11%	12%
Fourth line	9%	10%	10%	10%	10%	9%	11%	10%

b) within 6 months

	2010	2011	2012	2013	2014	2015	2016	2017
First line	4%	5%	4%	4%	4%	4%	5%	NA
Second line	12%	12%	13%	11%	13%	13%	14%	NA
Third line	14%	14%	13%	14%	14%	14%	15%	NA
Fourth line	15%	15%	14%	16%	14%	14%	14%	NA

c) within 12 months

	2010	2011	2012	2013	2014	2015	2016	2017
First line	6%	6%	6%	5%	6%	6%	6%	NA
Second line	17%	17%	18%	17%	18%	19%	19%	NA
Third line	20%	20%	18%	20%	20%	20%	20%	NA
Fourth line	21%	20%	18%	22%	20%	20%	19%	NA

Supplementary Table 4: Baseline characteristics of included and excluded patients (analysis of HbA_{1c} reduction at 6 months)

	First-line		Second-line		Third-line		Fourth-line	
	Included	Excluded	Included	Excluded	Included	Excluded	Included	Excluded
N	26295	23920	17124	14947	13428	11596	8560	8120
Baseline HbA_{1c} (mmol/mol)	71 (21)	73 (24)	75 (19)	75 (21)	76 (18)	77 (20)	79 (18)	80 (20)
Age at therapy (years)	62 (12)	62 (13)	63 (12)	63 (13)	64 (11)	64 (12)	64 (10)	64 (11)
Duration of diabetes (years)	2 (3)	2 (3)	5 (4)	5 (5)	8 (5)	8 (5)	10 (5)	11 (6)
Sex (% Male)	59%	58%	60%	58%	60%	58%	61%	57%
BMI (kg/m^2)	33 (7)	33 (7)	33 (7)	32 (7)	33 (7)	33 (7)	33 (7)	33 (7)
Weight (kg)	94 (21)	94 (22)	93 (21)	93 (22)	94 (21)	93 (23)	96 (21)	95 (22)
eGFR ($mL/min/1.73\ m^2$)	83 (18)	82 (19)	82 (20)	80 (22)	79 (22)	78 (23)	78 (22)	76 (23)
Systolic blood pressure (mmHG)	136 (15)	136 (16)	134 (14)	134 (15)	134 (15)	134 (15)	134 (15)	134 (15)
Diastolic blood pressure (mmHG)	79 (10)	80 (11)	78 (9)	78 (10)	77 (9)	77 (10)	76 (9)	76 (10)

Supplementary Table 5: 6 month weight change and risk of hypoglycemia with and without adjustment for drug as an additional covariate

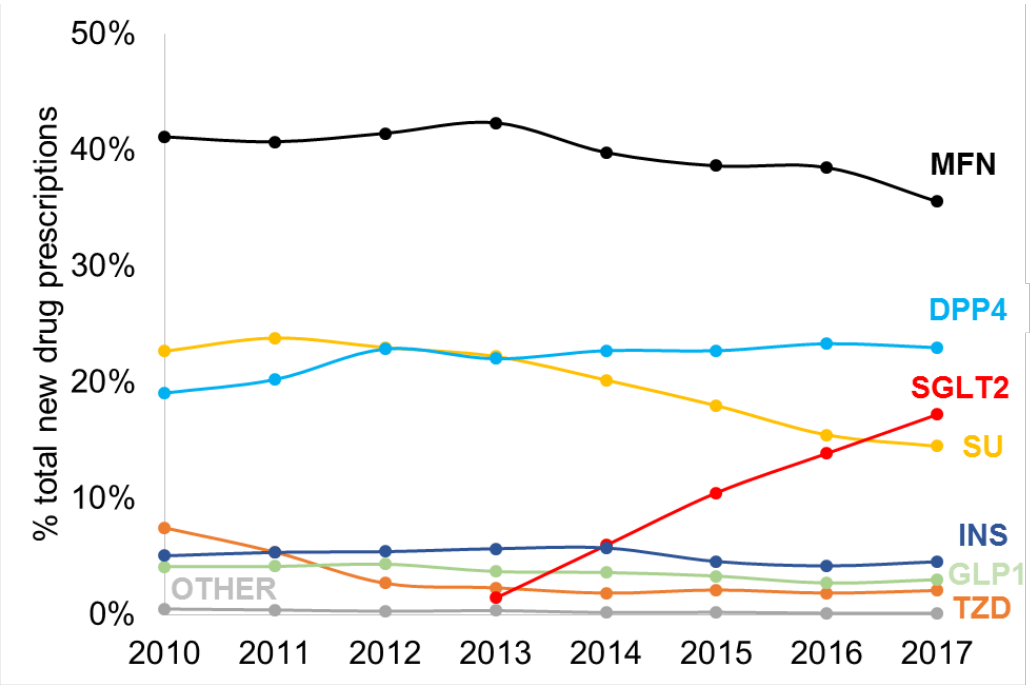
a) Weight change

Line of therapy	Annual weight change improvement (kg/year)	Drug adjusted annual weight change improvement (kg/year)
1st	-0.09 (-0.13;-0.15), p<0.001	-0.05 (-0.06;-0.05), p<0.001
2nd	-0.22 (-0.26;-0.18), p<0.001	-0.03 (-0.03;-0.02), p<0.001
3rd	-0.20 (-0.24;-0.15), p<0.001	-0.05 (-0.05;-0.04), p<0.001
4th	-0.20 (-0.26;-0.14), p<0.001	-0.04 (-0.05;-0.03), p<0.001

b) Risk of hypoglycemia

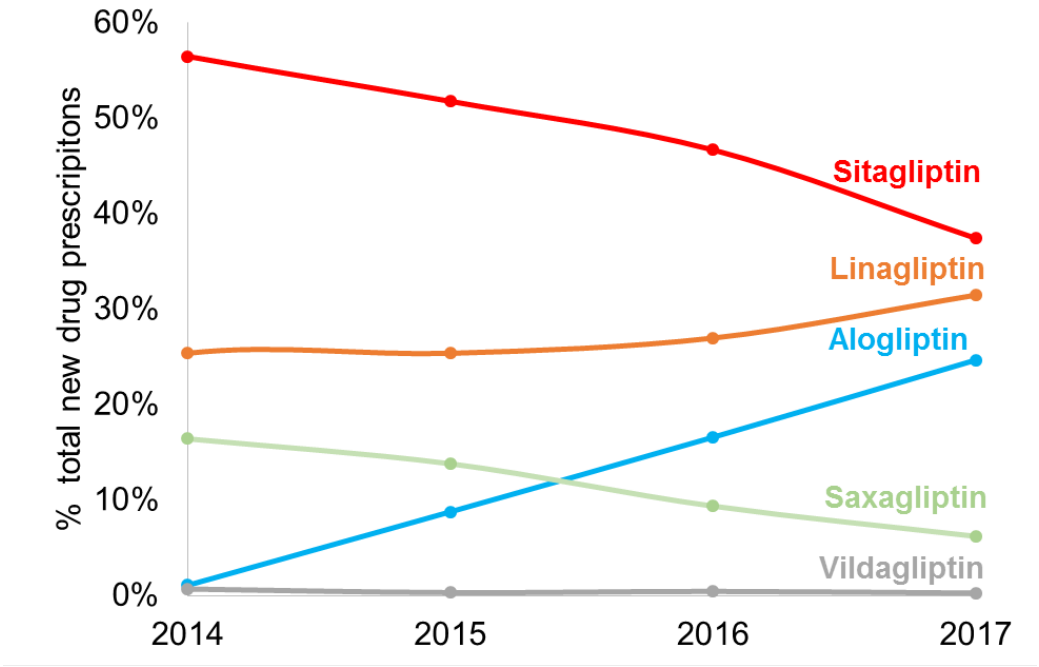
Line of therapy	Incidence rate ratio (per year)	Drug adjusted incidence rate ratio (per year)
1st	1.00 (0.93-1.08), p=0.99	1.01 (0.94-1.09), p=0.79
2nd	0.94 (0.88-1.00), p=0.04	0.98 (0.92-1.04), p=0.49
3rd	0.96 (0.90-1.02), p=0.21	1.02 (0.95-1.09), p=0.62
4th	0.95 (0.85-1.06), p=0.35	0.99 (0.88-1.12), p=0.90

Supplementary Figure 1: Time trends (2010-2017) in new drug prescriptions across lines 1-4of therapy (n=123,990). The prescriptions for each drug class each year are given as a percentage of total new drug prescriptions for that year.

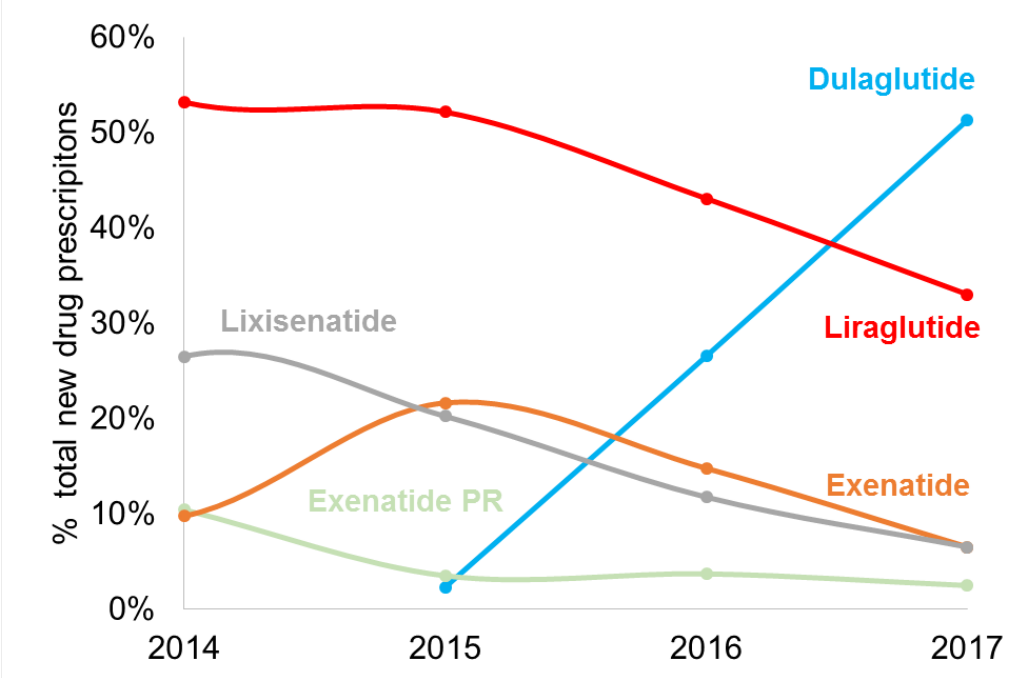


Supplementary Figure 2: Time trends (2014-2017) in new within class drug prescriptions across all lines of therapy for a) DPP4 inhibitors b) GLP-1 agonists c) SGLT2 inhibitors d) sulfonylureas. The prescriptions for each drug subtype each year are given as a percentage of total new prescriptions of the drug class for that year.

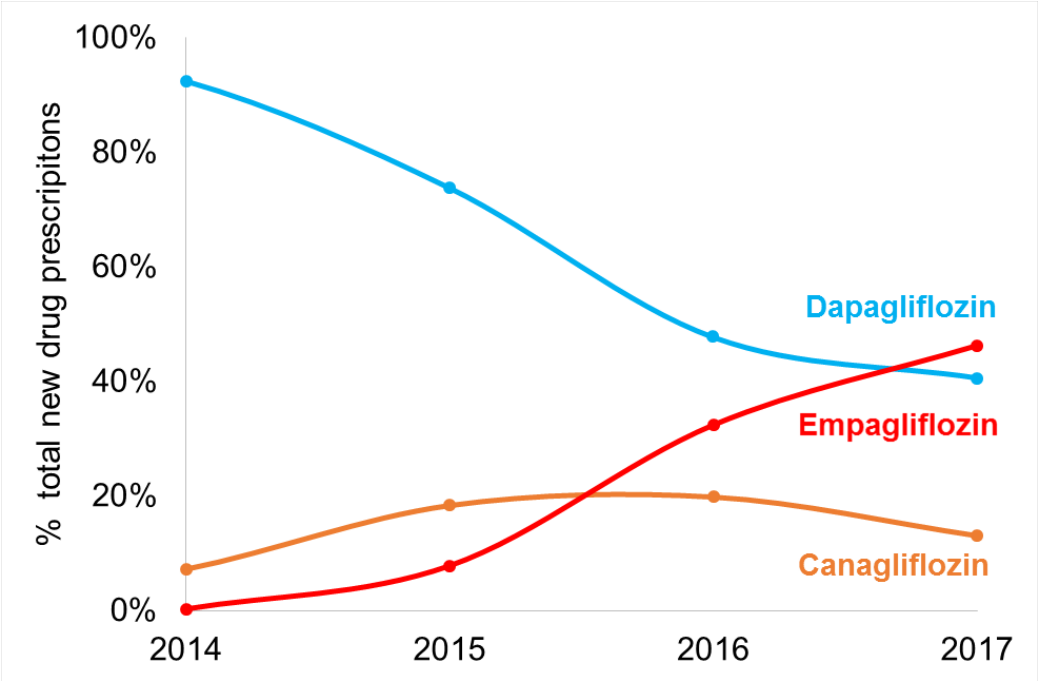
a) DPP4 inhibitors (n=29,835)



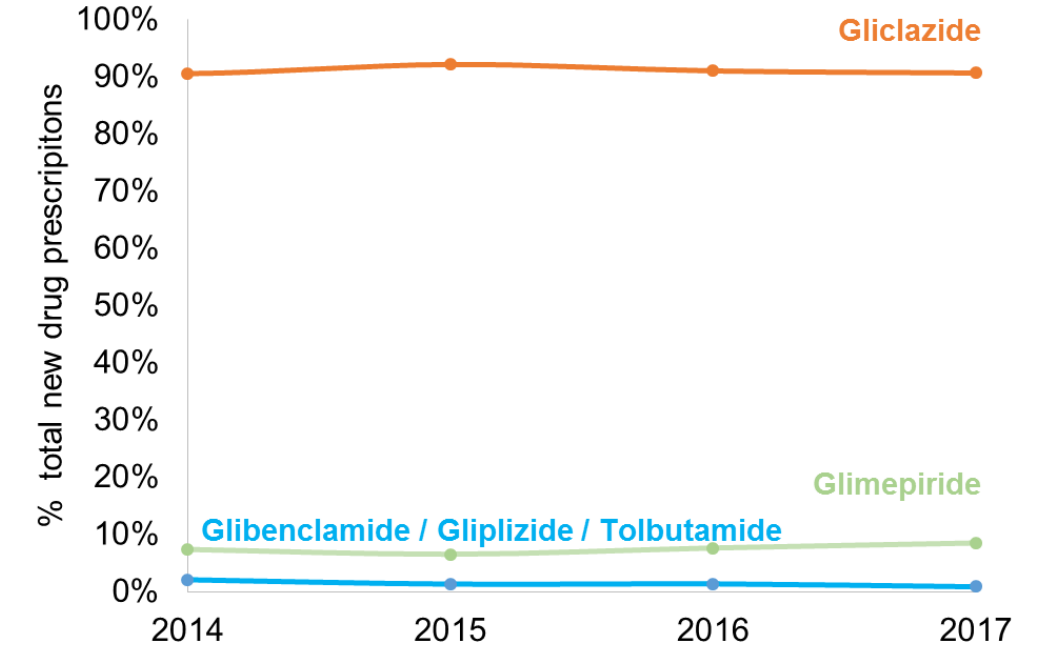
b) GLP-1 receptor agonists (n=6,989)



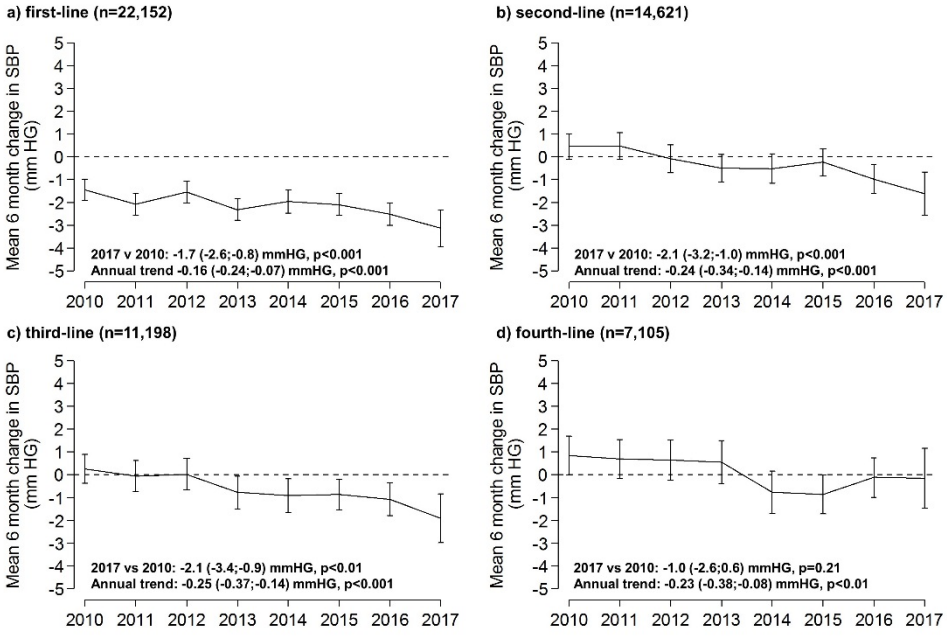
c) SGLT2 inhibitors (n=11,255)



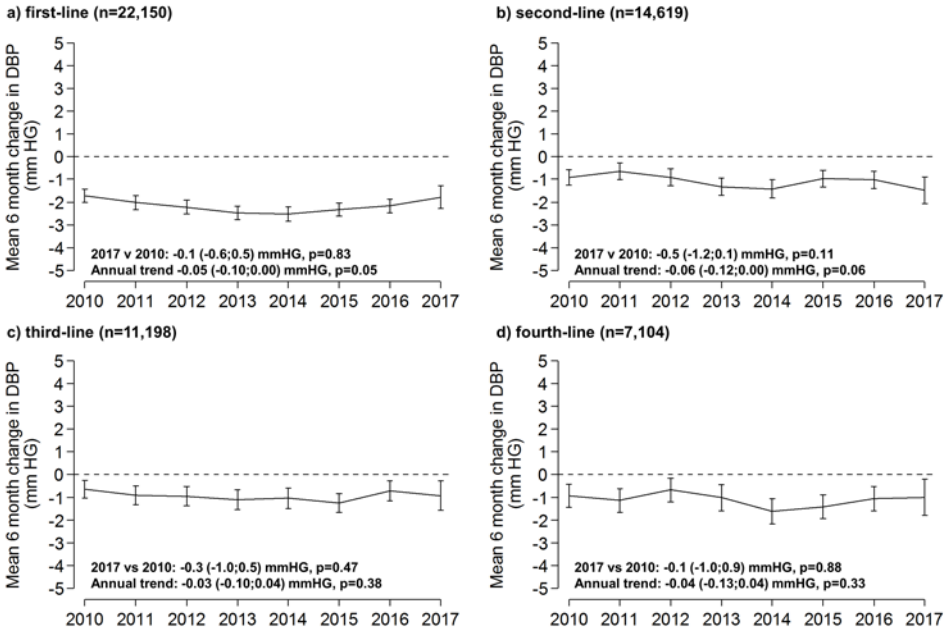
d) Sulfonylureas (n=24,506)



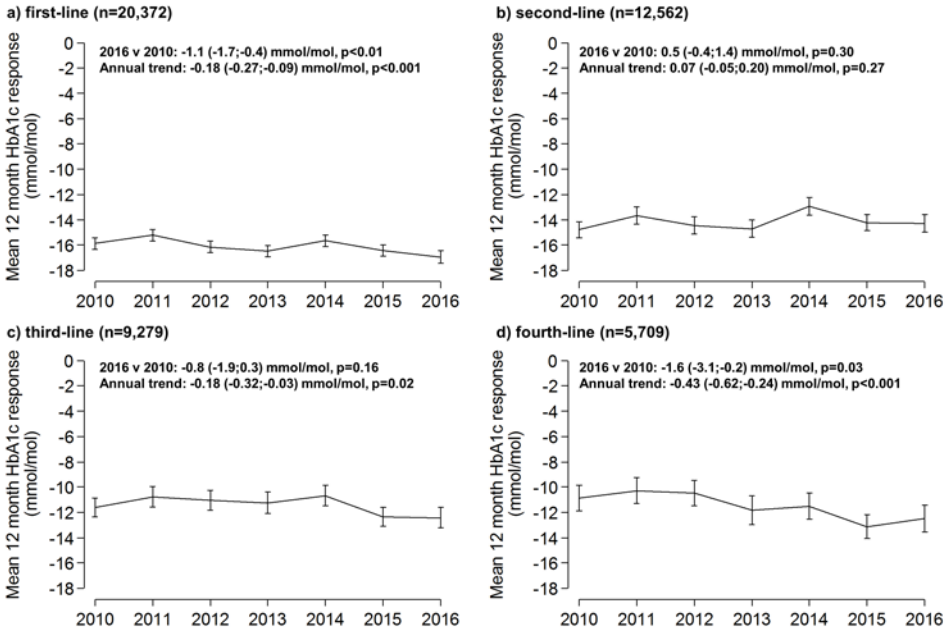
Supplementary Figure 3a: Mean change in systolic blood pressure (SBP) at 6 months, 2010-2017 for a) first-line b) second-line c) third-line d) fourth-line. Error bars are 95% confidence intervals. Data are standardised to the mean baseline systolic blood pressure, baseline HbA_{1c}, age at diagnosis and duration of diabetes over the entire study period, specific to each drug line.



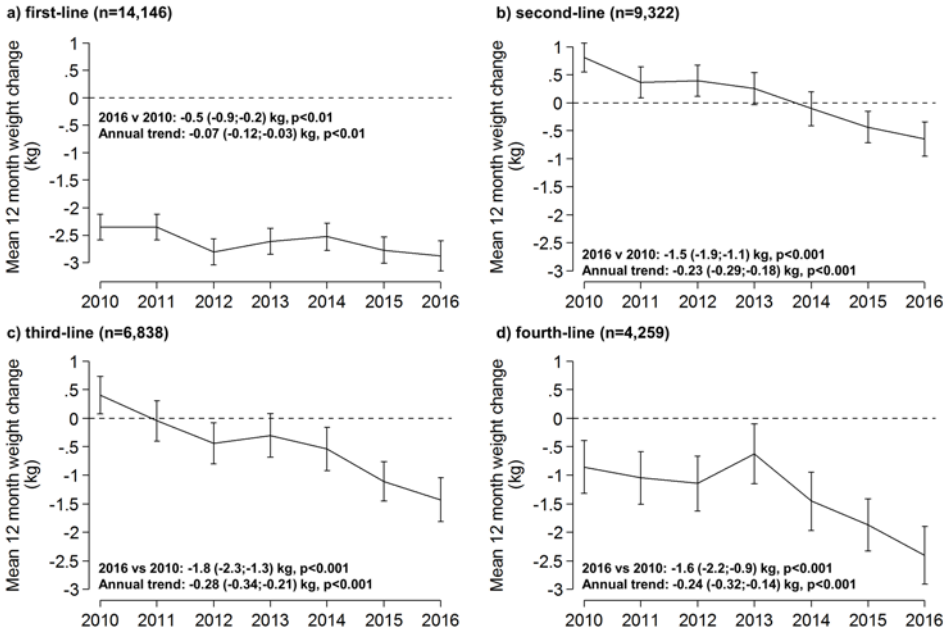
Supplementary Figure 3b: Mean change in diastolic blood pressure (DBP) at 6 months, 2010-2016 for a) first-line b) second-line c) third-line d) fourth-line therapy. Error bars are 95% confidence intervals. Data are standardised to the mean baseline diastolic blood pressure, baseline HbA_{1c}, age at diagnosis and duration of diabetes over the entire study period, specific to each drug line.



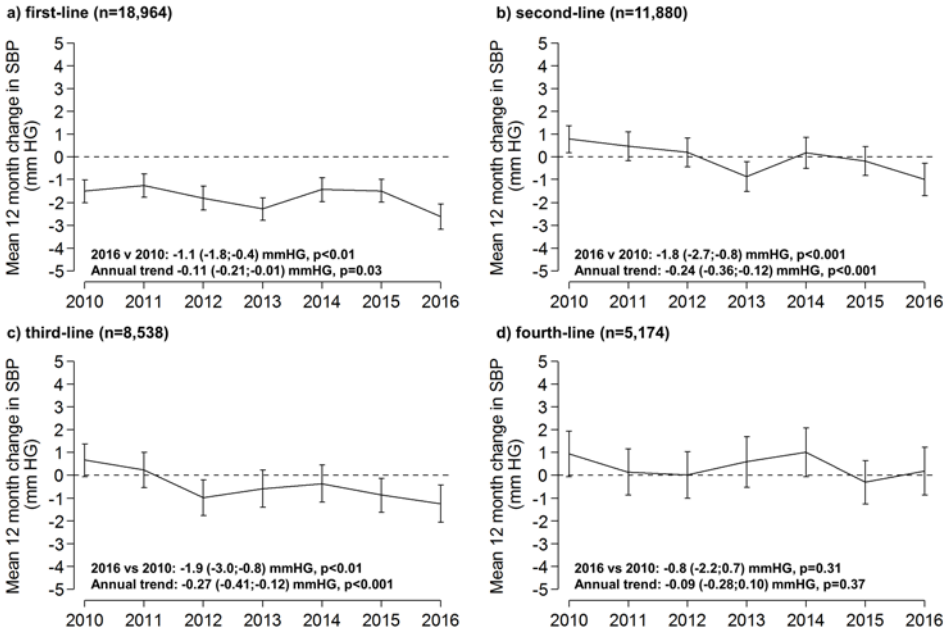
Supplementary Figure 4: Mean change in HbA_{1c} at 12 months, 2010-2016 for a) first-line b) second-line c) third-line d) fourth-line. Error bars are 95% confidence intervals. Data are standardised to the mean baseline HbA_{1c}, age at diagnosis and duration of diabetes over the entire study period, specific to each drug line.



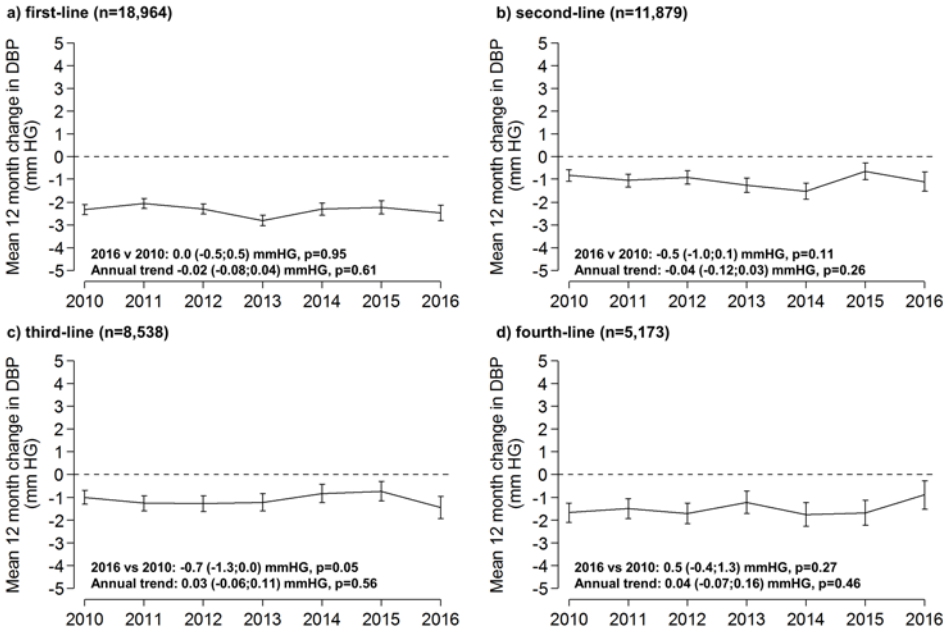
Supplementary Figure 5: Mean change in weight at 12 months, 2010-2016 for a) first-line b) second-line c) third-line d) fourth-line. Error bars are 95% confidence intervals. Data are standardised to the mean baseline weight, baseline HbA_{1c}, age at diagnosis and duration of diabetes over the entire study period, specific to each drug line.



Supplementary Figure 6a: Mean change in systolic blood pressure (SBP) at 12 months, 2010-2016 for a) first-line b) second-line c) third-line d) fourth-line. Error bars are 95% confidence intervals. Data are standardised to the mean baseline systolic blood pressure, baseline HbA_{1c}, age at diagnosis and duration of diabetes over the entire study period, specific to each drug line.

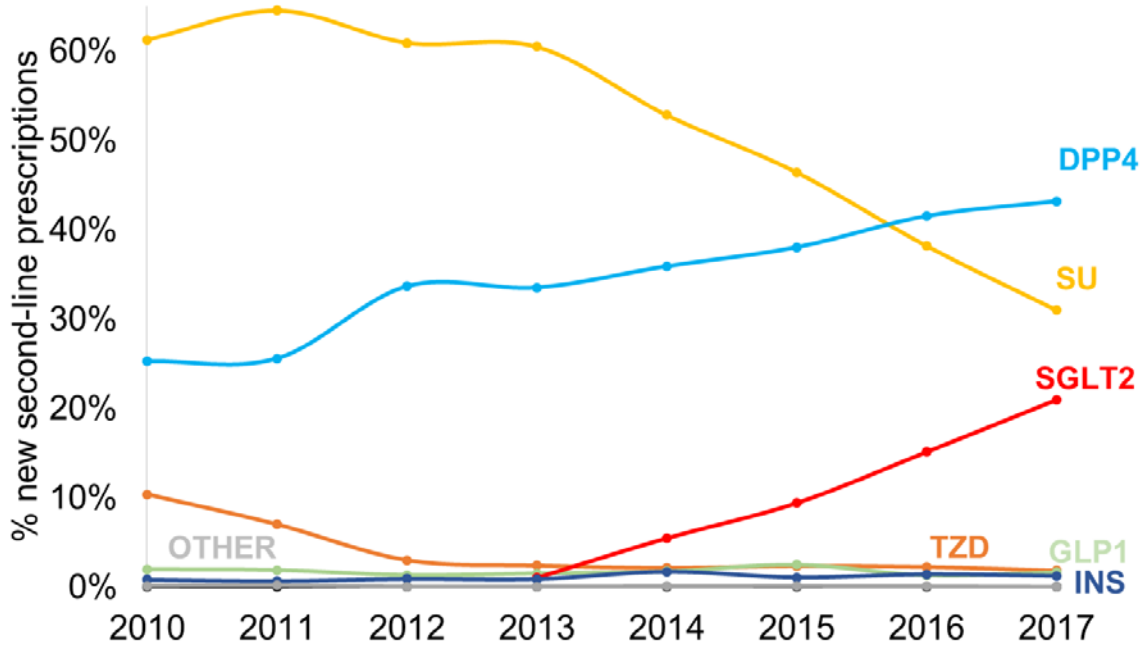


Supplementary Figure 6b: Mean change in diastolic blood pressure (DBP) at 12 months, 2010-2016 for a) first-line b) second-line c) third-line d) fourth-line therapy. Error bars are 95% confidence intervals. Data are standardised to the mean baseline diastolic blood pressure, baseline HbA_{1c}, age at diagnosis and duration of diabetes over the entire study period, specific to each drug line.

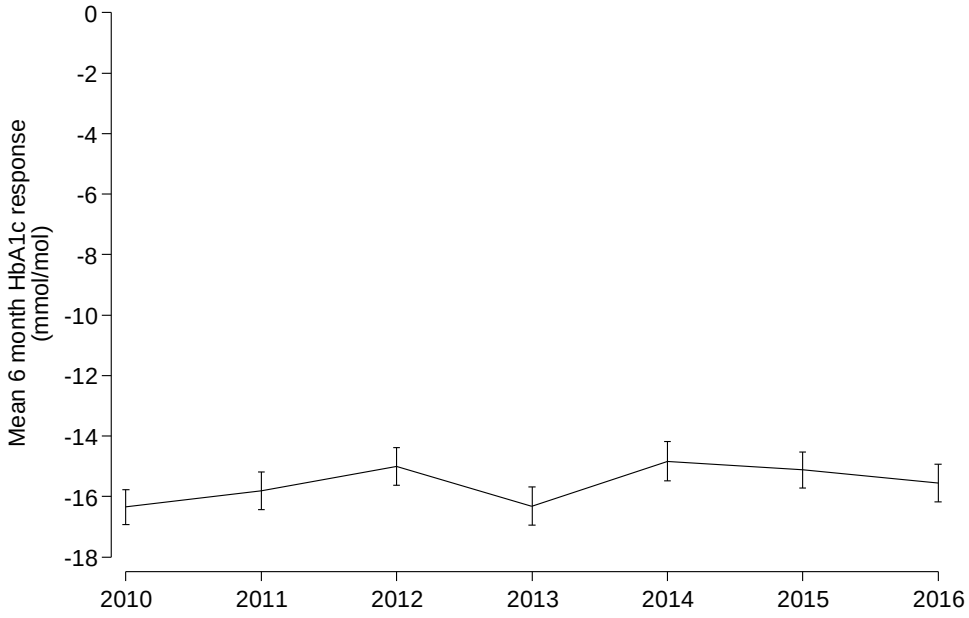


Supplementary Figure 7: Second-line prescribing trends and patient outcomes in the subset of patients adding a second-line drug to continued first-line metformin therapy (73% of patients included in the primary analysis)

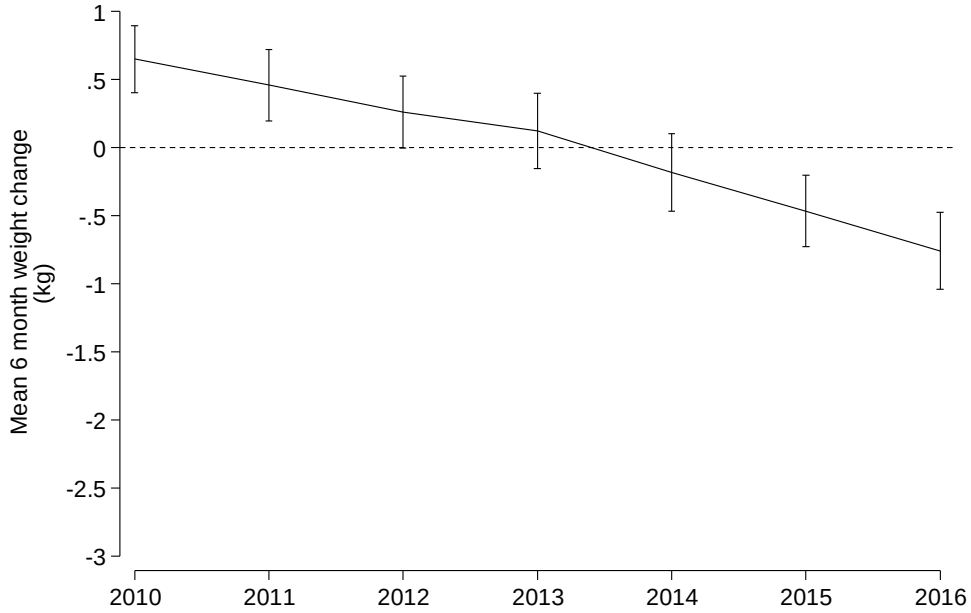
a) Time trends in new drug prescriptions. The prescriptions for each drug class each year are given as a percentage of total new drug prescriptions for that year.



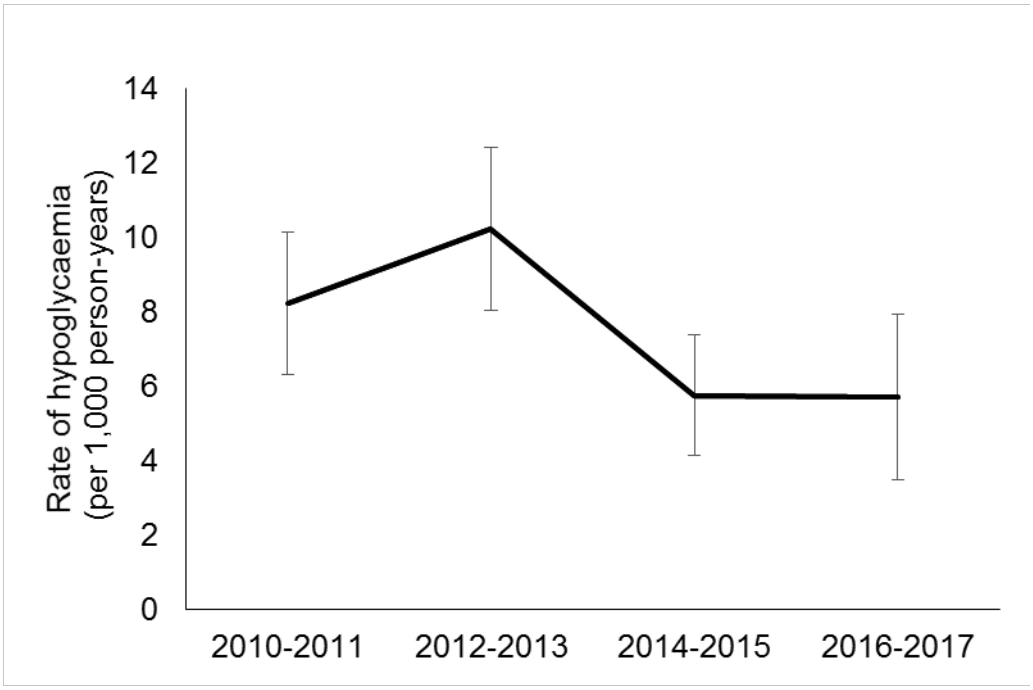
b) Mean change in HbA_{1c} at 6 months, 2010-2017. Error bars are 95% confidence intervals. Data are standardised to the average baseline HbA_{1c}, age at diagnosis and duration of diabetes in 2017.



c) Mean change in weight at 6 months, 2010-2017 for a) first-line b) second-line c) third-line d) fourth-line. Error bars are 95% confidence intervals. Data are standardised to the average baseline HbA_{1c}, age at diagnosis and duration of diabetes in 2017.



d) Hypoglycemia rates per 1,000 years by 2 year period. Rates represent the occurrence of hypoglycemia over the first two years after starting second-line therapy.



Chapter 3

Precision medicine in Type 2 diabetes: Clinical markers of insulin resistance are associated with altered short and long-term glycaemic response to DPP4 inhibitor therapy

John M. Dennis, Beverley M. Shields, Anita V. Hill, Bridget A. Knight, Timothy J. McDonald, Lauren R. Rogers, Michael N. Weedon, William E. Henley, Naveed Sattar, Rury R. Holman, Ewan R. Pearson, Andrew T. Hattersley, Angus G. Jones on behalf of the MASTERMIND consortium

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Acknowledgments of co-authors and contributions to paper

The Predicting Response to Incretin Based Agents (PRIBA) study was designed by Angus Jones, Tim McDonald, Bea Knight and Andrew Hattersley. Angus Jones obtained funding and ethical approval and set up and ran the study with the assistance of Anita Hill (project coordinator). Angus Jones and I designed this particular analysis. Beverley Shields, Lauren Rodgers and Michael Weedon extracted the CPRD data. I analysed the data with assistance from Beverley Shields, Angus Jones and William Henley. I drafted the manuscript, with assistance from Beverley Shields and Angus Jones. All authors provided support for the interpretation of results, critically revised the manuscript, and approved the final draft of the manuscript.

Abstract

Objective

A ‘precision’ approach to type 2 diabetes therapy would aim to target treatment according to patient characteristics. We examined if measures of insulin resistance and secretion were associated with glycaemic response to DPP4 inhibitor therapy.

Research Design and Methods

We evaluated whether markers of insulin resistance and insulin secretion were associated with 6 month glycaemic response in a prospective study of non-insulin treated participants starting DPP4 inhibitor therapy (PRIBA, n=254), with replication for routinely available markers in UK electronic healthcare records (CPRD, n=23,001). In CPRD we evaluated associations between baseline markers and 3 year durability of response. To test the specificity of findings we repeated analyses for GLP-1 receptor agonists (PRIBA n=339, CPRD n=4,464).

Results

In PRIBA markers of higher insulin resistance (higher fasting C-peptide ($p=0.03$), HOMA2 insulin resistance ($p=0.01$) and triglycerides ($p<0.01$)) were associated with reduced 6 month HbA_{1c} response to DPP4 inhibitors. In CPRD higher triglycerides and BMI were associated with reduced HbA_{1c} response (both $p<0.01$). A subgroup defined by obesity (BMI≥30kg/m^2) and high triglycerides (≥2.3mmol/L) had reduced 6 month response in both datasets (PRIBA HbA_{1c} reduction 5.3[95%CI 1.8,8.6]mmol/mol (0.5%) (obese, high triglycerides) vs 11.3[8.4,14.1] mmol/mol (1.0%) (non-obese, normal triglycerides), $p=0.01$. In CPRD the obese, high triglycerides subgroup also had less durable response (hazard ratio 1.28[1.16,1.41], $p<0.001$). There was no

association between markers of insulin resistance and response to GLP-1 receptor agonists.

Conclusions

Markers of higher insulin resistance are consistently associated with reduced glycaemic response to DPP4 inhibitors. This finding provides a starting point for the application of a precision diabetes approach to DPP4 inhibitor therapy.

PRIBA ClinicalTrials.gov identifier: NCT01503112

Introduction

Type 2 diabetes is a heterogeneous condition characterised by varying degrees of reduced beta cell function and higher levels of insulin resistance. Most of the 400 million people with type 2 diabetes worldwide will at some point require glucose lowering medication (1). Major international treatment guidelines recommend at least 4 oral treatment options after initial metformin has failed to achieve control, with choice between these informed predominantly by method of administration, overall side effect profile and cost (2-5).

Individual response to glucose lowering therapies in type 2 diabetes varies greatly. Identification of clinical phenotypic features or biomarkers robustly associated with glycaemic response or other potentially beneficial effects for example reduced weight gain, or side effects for each therapy, may allow treatment of people with the agent that is most likely to be effective for them, an approach known as ‘precision’ or ‘stratified’ medicine (6, 7). While much research has focused on identifying genetic or novel biomarker predictors of response, precision diabetes is most likely to be cost effective and have clinical impact using simple inexpensive biomarkers or routinely available clinical phenotypic features (8, 9).

DPP4 inhibitors are common (20% of U.S. and 40% of UK second-line prescriptions in 2016) (10) (J.M Dennis, B.M Shields, personal communication), well-tolerated (11), oral therapy options recommended in all clinical guidelines (2-5). Beyond baseline HbA_{1c} and fasting glucose it is unclear if other factors are associated with glycaemic response to DPP4 inhibitors (12, 13). A major mechanism of action of DPP4 inhibitors is potentiation of beta cell insulin secretion. We aimed to establish if measures of insulin secretion and insulin resistance were associated with short-term glycaemic response and long-term

durability of response in people with type 2 diabetes starting DPP4 inhibitor therapy.

Research Design and Methods

We assessed whether clinical features and biomarkers associated with insulin secretion and insulin resistance were predictive of short-term 6 month glycaemic response in analysis of a prospective study of people starting DPP4 inhibitor therapy as part of routine care (PRIBA). To validate our findings we tested the consistency of associations between routinely recorded factors associated with response in PRIBA in a retrospective analysis of a much larger group of people from UK Clinical Practice Research Datalink (CPRD), evaluating both 6 month glycaemic response and long term durability of response to 3 years.

Study setting and assessment

PRIBA prospective study

The PRIBA study was designed to test the hypothesis that those who have low insulin secretion, as measured by C-peptide, will have poor glycaemic response to incretin based treatments (https://clinicaltrials.gov/ct2/show/NCT01503112), with associations between glycaemic response and other clinical features, islet autoantibodies and Homeostasis Model Assessment (HOMA) 2 estimates of beta cell function and insulin sensitivity evaluated in pre-specified secondary analysis. 305 participants due to start DPP4 inhibitor therapy as part of their usual care were recruited from primary and secondary care across 17 National Institute of Health Research (NIHR) clinical research network centres in the UK from April 2011 to October 2013 as previously described (14).

At baseline (immediately prior to starting therapy) we measured *HbA$_{1c}$*, fasting glucose, clinical markers of insulin resistance and insulin secretion (fasting C-peptide and post meal urine C-peptide Creatinine ratio (UCPCR) (15, 16); BMI, triglycerides and HDL-cholesterol (HDL-c) (17); sex-hormone binding globulin (SHBG), GAD and IA2 islet autoantibodies) and other clinical characteristics (age at therapy, sex, duration of diabetes, eGFR, ethnicity, LDL-cholesterol (LDL-c), number of diabetes therapies). We calculated HOMA-estimates of beta-cell function (HOMA2%B) and insulin resistance (HOMA2 IR) from fasting glucose and C-peptide measures using the HOMA2 calculator available from http://www.dtu.ox.ac.uk/homacalculator/ (18). Laboratory analysis was conducted as previously reported (14). Participants were included in the analysis if they were not insulin treated and had at least 3 months follow up with >75% adherence to therapy and limited co-treatment change (see study profile supplementary figure 1a). Ethics approval was granted by the South West National Research Ethics committee, and all participants gave written informed consent.

Retrospective analysis of UK primary care data (CPRD database)

CPRD is the world's largest longitudinal database of anonymised primary care electronic health records (19). We included 23,001 non-insulin treated people with type 2 diabetes with prescription records of starting a DPP4 inhibitor for the first time from June 2007 to September 2016, and followed them up whilst they remained on DPP4 inhibitor therapy without the addition or cessation of any other anti-hyperglycaemic medication (see study profile supplementary figure 1b). We extracted baseline routine clinical characteristics (age at therapy, duration of diabetes, sex and BMI) and biomarkers (HbA$_{1c}$, triglycerides, HDL-c, LDL-c and eGFR), with baseline defined as the most recent record in the 3

months prior to the drug start date. Ethics approval was granted by the CPRD Independent Scientific Advisory Committee (ISAC 13_177R).

Analysis

Outcome definitions

Short-term glycaemic response (PRIBA & CPRD)

The primary outcome was the absolute change from baseline in HbA_{1c} 6 months after starting therapy, adjusting for baseline HbA_{1c}. Where a 6 month HbA_{1c} was not available or eligible in the PRIBA study (see supplementary figure 1a) we used a 3 month HbA_{1c} measure, as previously described (14). In CPRD a valid 6 month HbA_{1c} was defined as the closest HbA_{1c} to 6 months after the drug start date +/-3 months for people on unchanged anti-hyperglycaemic therapy.

Durability of glycaemic response (CPRD)

In CPRD where long-term follow-up data were available we assessed durability of response as the time to glycaemic failure over 3 years in a complete case analysis of people with baseline HbA_{1c} between 53-97 mmol/mol (7-11%) and at least 3 months on DPP4 inhibitor therapy (n=15,616). Glycaemic failure was defined as ***a)*** two consecutive HbA_{1c}'s greater than 69 mmol/mol (8.5%) ***b)*** a single HbA_{1c} greater than 69 mmol/mol (8.5%) followed by the addition of another anti-hyperglycaemic therapy. To examine the sensitivity of results to this definition we repeated the analysis using HbA_{1c} thresholds of a) 53mmol/mol (7.5%) and b) the baseline HbA_{1c} level specific to each individual patient.

Statistical analysis

Short-term response (PRIBA & CPRD)

We examined associations between each standardised marker of insulin resistance and insulin secretion and 6 month HbA_{1c} response in a series of linear regression models adjusted for baseline HbA_{1c} and, in PRIBA, co-therapy change (12, 19). Non-normally distributed variables were log-transformed. We conducted a complete case analysis for each marker, including all people with valid data even if they had missing data for other markers. To evaluate model fit we examined normality of residuals and linearity of associations for continuous variables. In both datasets we tested the independence of initial associations for each marker of insulin resistance and insulin secretion with 6 month response in further multivariable analysis, controlling for baseline HbA_{1c} and other routinely recorded characteristics: age at therapy, duration of diabetes, sex, eGFR, LDL-c, ethnicity (CPRD only: white, non-white, missing) and co-therapy change (PRIBA only, CPRD people all on unchanged therapy).

To further assess the robustness of findings we repeated the baseline adjusted analysis of 6 month response for males and females separately in both datasets, and in PRIBA with additional adjustment for fasting glucose. In CPRD we repeated the baseline adjusted analysis using 12 month response as the outcome in a distinct cohort of people with 12 month (closest +/-3 months as for definition of 6 month response) HbA_{1c} record (n=16,166).

Subgroup analysis of short-term response (PRIBA & CPRD)

Based on the initial results we defined 3 patient subgroups by standard clinical cut-offs for obesity (BMI>=30 kg/m^2) and high triglycerides (>=2.3mmol/L) (20) - *Group A*: non-obese and normal triglycerides, *Group B*: non-obese OR normal

triglycerides, *Group C*: obese and high triglycerides. We estimated the mean 6 month HbA_{1c} response for each subgroup using linear regression models adjusted for baseline HbA_{1c} and, in PRIBA, co-therapy change. We standardised baseline HbA_{1c} to the mean PRIBA baseline level of 74mmol/mol (8.9%) for all subgroups in both datasets.

Durability of response (CPRD)

For three subgroups defined by the same BMI and triglyceride thresholds we compared mean durability in response to three years after starting therapy using a flexible parametric time to failure survival model. We included all people with at least three months on therapy after starting a DPP4 inhibitor with valid baseline records of all covariates (baseline HbA_{1c}, age at therapy, duration of diabetes, sex and eGFR). The use of flexible parametric models allowed prediction of the probability of therapy failure over three years as well as hazard ratios consistent with Cox proportional hazards regression (21). We tested continuous variables for non-linearity, and evaluated proportional hazards assumptions using Schoenfeld residuals. To estimate the probability of therapy failure (the inverse of survival) for each subgroup a predicted survival curve was calculated for each patient in the dataset before the individual survival curves for all people within a subgroup were averaged (22). Each curve was standardised to the mean CPRD values of other clinical covariates (baseline HbA_{1c} = 72mmol/mol (8.7%), age at therapy = 64 years, duration of diabetes = 8 years, eGFR = 82 ml/min/1.73m^2). Point estimates for the failure probability at 3 years by subgroup were calculated using the same approach.

Replication analysis with GLP-1 receptor agonists (PRIBA and CPRD)

To test the specificity of findings for DPP4 inhibitors we repeated the analyses of short-term response and durability of response for non-insulin treated subjects starting GLP-1 receptor agonists, the other glucose-lowering drug evaluated in PRIBA (PRIBA n=339, CPRD n=4,464). We have previously reported the PRIBA primary analysis of predictors of glycaemic response for the full PRIBA GLP-1 receptor agonist cohort, which included an additional 209 insulin treated participants (14). All data extraction and analysis were conducted using Stata v14.0 (StataCorp, College Station, TX).

Results

Patient characteristics & response to DPP4 inhibitor therapy

Baseline characteristics and biomarker measures were similar for subjects starting DPP4 inhibitors in both datasets (Table 1). In both cohorts the majority of people started Sitagliptin. 254 people were included in PRIBA and 23,001 (for analysis of 6 month glycaemic response) in CPRD (for study profiles see supplementary figure 1). Mean (standard deviation (SD)) 6 month HbA_{1c} change was -8.3 (13.5) mmol/mol (-0.7% (1.2%)) in PRIBA and -7.6 (15.1) mmol/mol (-0.7% (1.4%)) in CPRD.

Table 1: Subject baseline characteristics

	PRIBA (n=254)	CPRD (n=23,001)
Characteristics mean (SD) unless stated		
Baseline HbA1c (mmol/mol)	74 (12)	72 (15)
Baseline HbA1c (%)	8.9 (1.1)	8.7 (1.3)
Age at therapy start (years)	63 (10)	64 (11)
Age at diagnosis (years)	54 (10)	56 (10)
Male sex (%)	63%	61%
Duration of diabetes (years)	9 (6)	8 (5)
BMI - median (IQR); mean(SD)	32 (29-37); 33 (6)	32 (28-36); 33 (6)
Ethnicity (%)		
White	97%	45%
Non-White	3%	6%
Missing	0%	49%
Biomarkers median (IQR); mean (SD) unless stated *=log-transformed		
Triglycerides (mmol/L)	1.7 (1.2-2.4); 1.8 (0.9)*	1.8 (1.3-2.6); 1.9 (1.0)*
HDL-c (mmol/L)	1.1 (0.9-1.3); 1.1 (0.3)*	1.1 (0.9-1.3); 1.1 (0.3)*
LDL-c (mmol/L)	1.9 (1.5-2.3); 1.9 (0.8)*	2.1 (1.6-2.6); 2.0 (0.8)*
SHBG (nmol/L)	27 (19-41); 27 (16)*	NA
Fasting C-peptide (pmol/L)	1150 (820-1460); 1090 (480)*	NA
HOMA2-%B	54 (37-73); 51 (27)*	NA
HOMA2 IR	3.1 (2.3-4.2); 3.1 (1.5)*	NA
UCPCR nmol/mmol	3.4 (2.0-5.0); 3.0 (2.3)*	NA
eGFR (ml/min/1.3m^2)	85 (70-98); 85 (24)	82 (66-97); 82 (23)
GAD or IA2 positive (%)	3%	NA
Therapy		
Number of concomitant therapies at therapy start (% of total)		
0	3%	6%
1	35%	51%
2	57%	42%
3+	5%	2%
DPP4 type (% of total)		
Sitagliptin	87%	72%
Alogliptin	0%	2%
Linagliptin	4%	10%
Saxagliptin	6%	12%
Vildagliptin	2%	4%

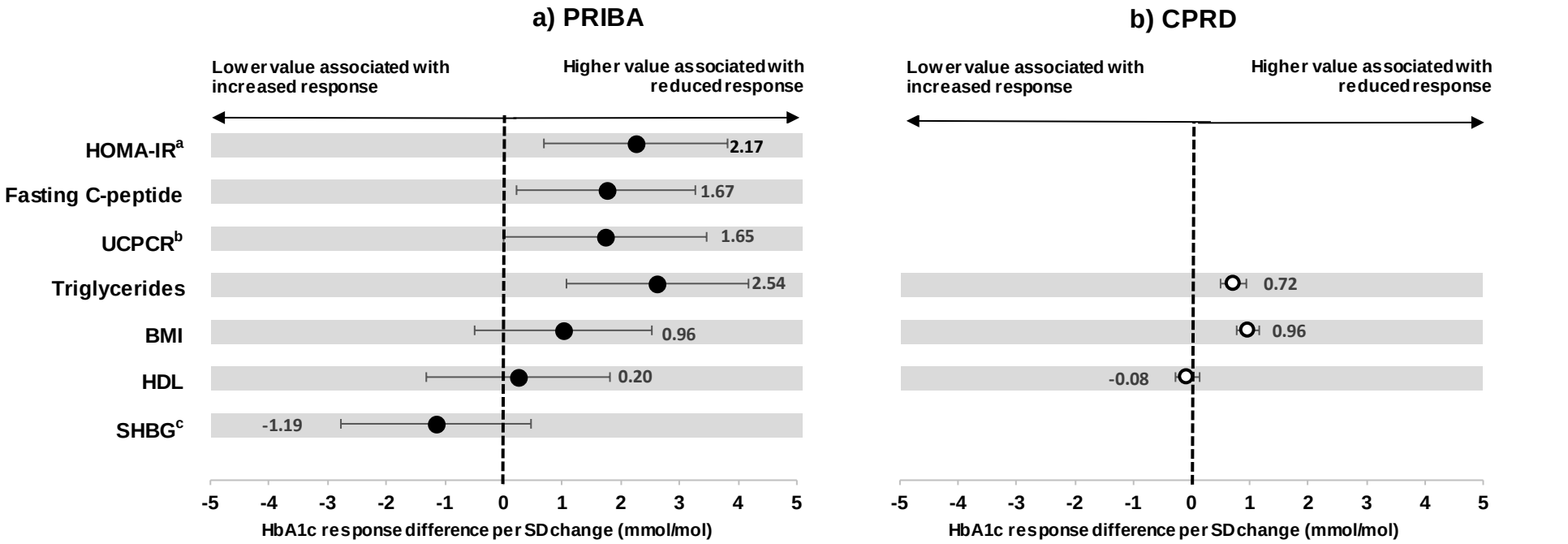
Higher baseline fasting C-peptide and HOMA measured insulin resistance are associated with reduced glycaemic response to DPP4 inhibitors

In the PRIBA cohort mean HbA_{1c} response was reduced by 1.67 mmol/mol for every 1 SD higher baseline fasting C-peptide (standardised β 1.67 [95% CI 0.17 to 3.17] mmol/mol/SD, p=0.03) (Figure 1). We observed the same direction and similar size of effect for UCPCR (response reduction per SD higher 1.65 [95% CI -0.07 to 3.37] mmol/mol, p=0.06). Higher baseline HOMA measured insulin resistance (HOMA2-IR) was also associated with reduced response (response reduction per SD higher: 2.17 [95% CI 0.62 to 3.72], mmol/mol, p=0.01), but there was no evidence of an association between beta-cell function (HOMA2-%B) and response (response reduction per SD higher 0.16 [95% CI -1.49 to 1.81] mmol/mol, p=0.85). Islet autoantibody prevalence was low (2.8% GAD or IA2 positive; response reduction for presence of autoantibodies: 5.6 [95% CI -3.6, 14.7] mmol/mol, p=0.23).

Other markers of insulin resistance are consistently associated with glycaemic response to DPP4 inhibitors in PRIBA and CPRD

In PRIBA higher triglycerides was associated with reduced glycaemic response (response reduction per SD increase 2.54 [95% CI 0.99 to 4.08] mmol/mol, p<0.001), with a consistent direction of association for higher BMI (response reduction per higher BMI 0.96 [95% CI -0.54 to 2.46] mmol/mol, p=0.21) and lower SHBG (response reduction per SD higher SHBG -1.19 [95% CI -2.81 to 0.42] mmol/mol, p=0.15) (Figure 1, supplementary table 1). In CPRD higher triglycerides and BMI were associated with reduced HbA_{1c} response (Figure 1, supplementary table 1). HDL-c was not associated with response in either dataset (p=0.81 in PRIBA, p=0.46 in CPRD).

Figure 1: DPP4 inhibitors - associations between markers of insulin resistance and HbA1c response at 6 months. Circles (black = PRIBA, white = CPRD) denote the mean HbA1c change (mmol/mol) at 6 months per 1 standard deviation (SD) higher baseline value of each marker. Error bars denote 95% confidence intervals.



[a] HOMA2 measured insulin resistance [b] UCPCR = post meal urine C-peptide Creatinine ratio [c] SHBG = sex-hormone binding globulin

Markers of insulin resistance are associated with glycaemic response to DPP4 inhibitors independently of other routine clinical characteristics

Results were consistent when *a)* stratifying by sex (supplementary table 1), *b)* controlling for baseline HbA_{1c}, age at therapy, sex, duration of diabetes, eGFR, LDL-c, ethnicity (CPRD only) and co-therapy change (PRIBA only) in multivariable analysis of each dataset (supplementary table 2), *c)* in PRIBA controlling for fasting glucose (supplementary table 3) and *d)* in CPRD with 12 month HbA_{1c} response as the outcome (supplementary table 4).

Standard clinical criteria of obesity and high triglycerides can identify people ***likely to have markedly reduced glycaemic response to DPP4 inhibitors***

Higher triglycerides was associated with reduced glycaemic response independently of BMI in both datasets, and higher BMI was associated with reduced response independently of triglycerides in CPRD (supplementary table 5). To examine the potential clinical implication of this finding we compared mean baseline HbA_{1c} adjusted response in 3 patient subgroups defined by standard clinical cut-offs for obesity (BMI>=30 kg/m^2) and high triglycerides (>=2.3mmol/L) - *Subgroup A*: non-obese and normal triglycerides, *Subgroup B*: non-obese OR normal triglycerides, *Subgroup C*: obese and high triglycerides).

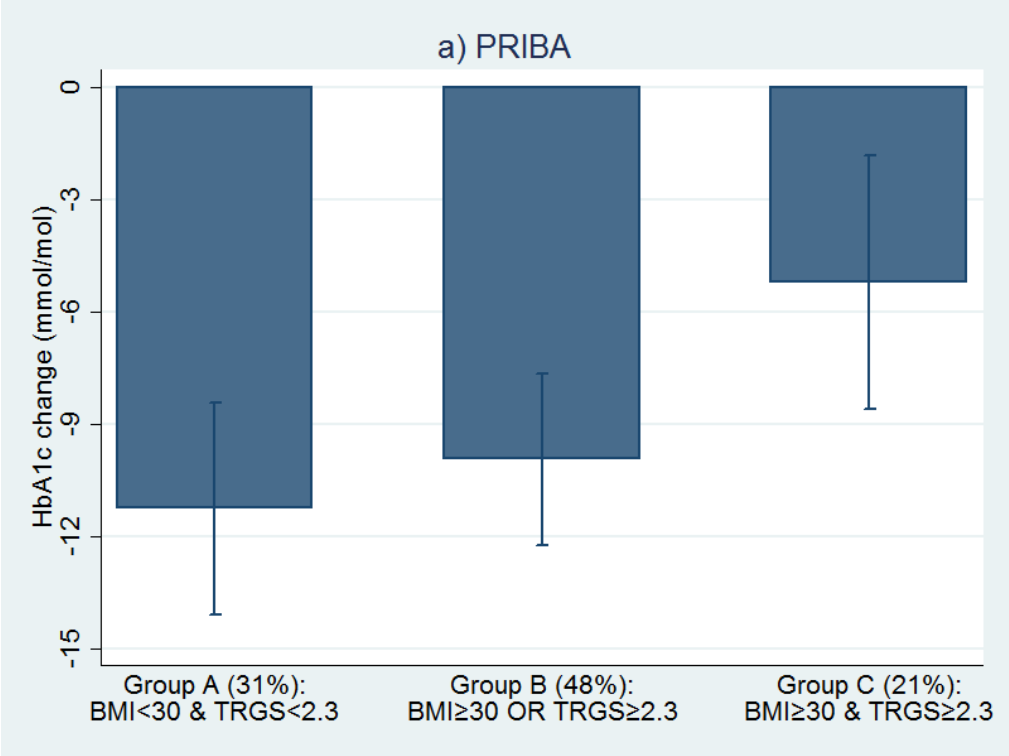
In PRIBA we found mean 6 month baseline HbA_{1c} standardised glycaemic response was halved for the obese and high triglycerides subgroup (Subgroup C -5.2 [95% CI -1.8 to -8.6] mmol/mol (-0.5% [95% CI -0.2;-0.8])) compared to the non-obese and normal triglycerides subgroup (Subgroup A -11.3 [95% CI -8.4 to -14.1] mmol/mol (-1.0% [95% CI -0.8;-1.3])) and was significantly reduced compared to intermediate Subgroup B (-9.9 [95% CI -7.6 to -12.2] mmol/mol (-

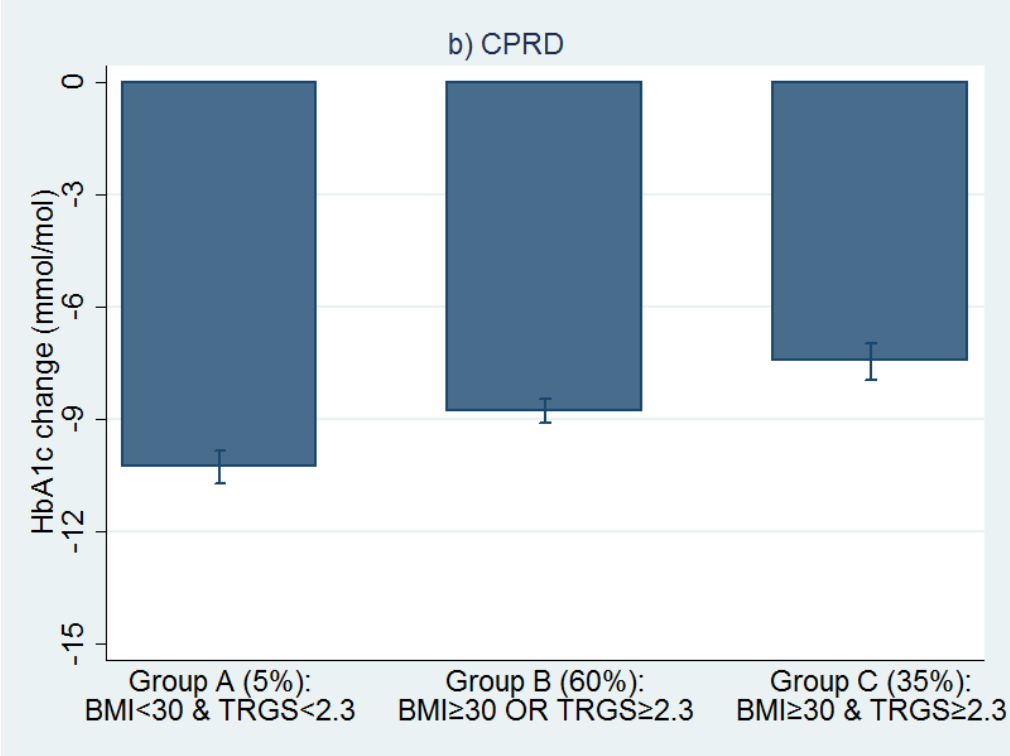
0.9% [95% CI -0.7;-1.1])) (Figure 2a). Direction of effect was replicated in CPRD, albeit with smaller differences in mean response between subgroups (Subgroup A mean baseline adjusted HbA_{1c} response -10.3 [95% CI -9.8 to -10.7] mmol/mol (-0.9% [95% CI -0.9;-1.0]), Subgroup B -8.8 [95% CI -8.5 to -9.1] mmol/mol (-0.8% [95% CI -0.8;-0.8]), Subgroup C -7.5 [95% CI -7.0 to -7.9] mmol/mol (-0.7% [95% CI -0.6;-0.7]), Figure 2b).

Obesity and high triglycerides are associated with less durable glycaemic response to DPP4 inhibitors over 3 years

15,616 people were followed up in this analysis for a mean time of 1.5 years. Over the 3 year study period 3,514 (23%) people had glycaemic failure (confirmed HbA1c ≥ 69 mmol/mol (8.5%). We observed an increased relative risk of glycaemic failure , reflecting a less durable response) in the same obesity and high triglycerides defined subgroups, standardising for other clinical characteristics (hazard ratios for glycaemic failure: Subgroup C obese AND high triglycerides versus Subgroup A non-obese and normal triglycerides 1.28 [95% CI 1.16-1.41], p<0.001; Subgroup B obese OR high triglycerides versus Subgroup A 1.17 [95% CI 1.08-1.27], p<0.001; Subgroup C versus Subgroup B 1.09 [95% CI 1.01-1.18], p=0.04; supplementary table 6). Consistent relative differences between subgroups were observed at HbA_{1c} failure thresholds of 7.5% and the baseline HbA_{1c} specific to each individual patient (supplementary table 7-8). These results translated into significant differences between subgroups in the absolute probability of glycaemic failure at three years (Subgroup C: obese AND high triglycerides 39% [95% CI 37-42%]; Subgroup B: obese OR high triglycerides 37% [95% CI 35-38%]; Subgroup A: non-obese and normal triglycerides 32% [95% CI 31-34 %] supplementary figure 2).

Figure 2: DPP4 inhibitors - predicted mean absolute HbA1c change from baseline at 6 months in a) PRIBA b) CPRD across subgroups defined by the presence or absence of obesity (BMI>=30 kg/m^2) and high triglycerides (TRGs >=2.3mmol/L) - *Subgroup A*: non-obese and normal triglycerides, *Subgroup B*: non-obese OR normal triglycerides, *Subgroup C*: obese and high triglycerides. Baseline HbA1c is standardised to the mean PRIBA baseline level of 74mmol/mol (8.9%) for all subgroups. Error bars denote 95% confidence intervals.

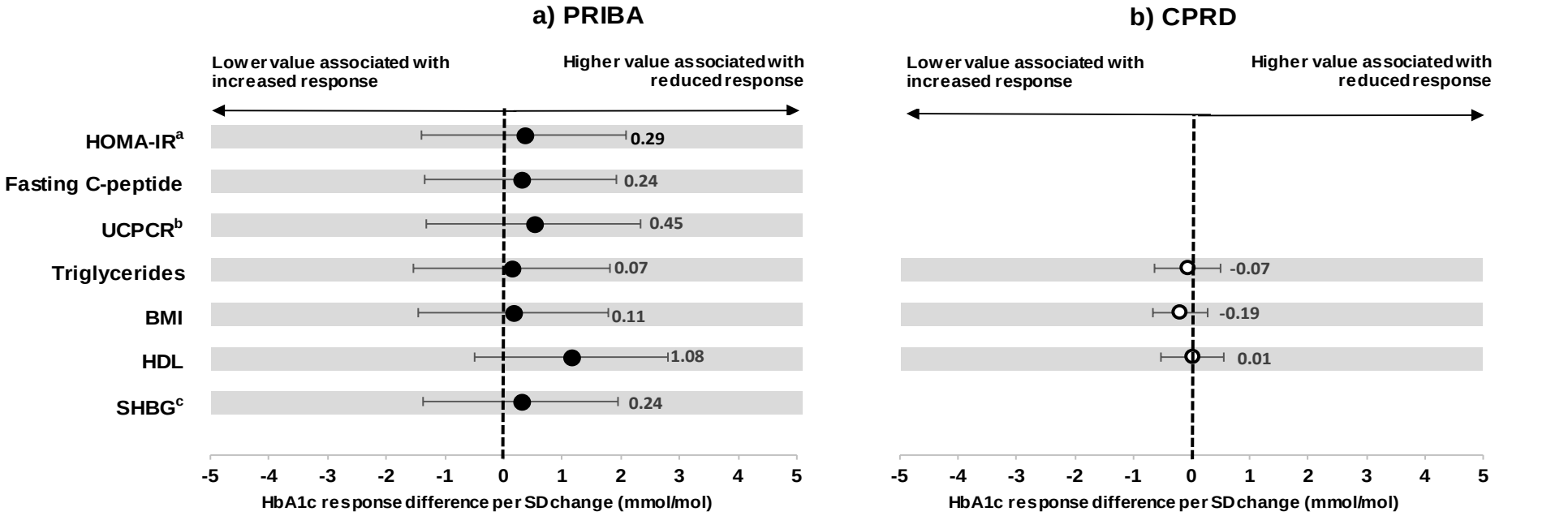




There is no evidence of an association between markers of insulin resistance and glycaemic response to GLP-1 receptor agonists

We found no evidence of an association between any marker of insulin resistance and 6 month glycaemic response to GLP-1 receptor agonists in PRIBA (n=339) or CPRD (n=4,464) on continuous analysis (Figure 3, supplementary tables 8-9). There was also no evidence for a difference in response to GLP-1 receptor agonists across the obesity and triglyceride defined subgroups (all subgroup comparisons p>0.40; supplementary table 10, supplementary figure 3), although there were few subjects in the non-obese, normal triglyceride subgroup starting GLP-1 receptor agonist therapy in both datasets (PRIBA 2%, CPRD 5%). Similarly, in CPRD we found no evidence of an association between durability of glycaemic response and BMI (HR per unit increase 1.01 (95% CI 1.00-1.02, p=0.29) or triglyceride levels (HR per unit increase 0.99 (95% CI 0.95-1.04, p=0.80) (supplementary table 11), or of a difference in durability of response across obesity and triglyceride defined subgroups (supplementary table 12, supplementary figure 4).

Figure 3: GLP-1 receptor agonists - associations between markers of insulin resistance and HbA1c response at 6 months. Circles (black = PRIBA, white = CPRD) denote the mean HbA1c change (mmol/mol) at 6 months per 1 standard deviation (SD) higher baseline value of each marker. Error bars denote 95% confidence intervals.



[a] HOMA2 measured insulin resistance [b] UCPCR = post meal urine C-peptide Creatinine ratio [c] SHBG = sex-hormone binding globulin

Conclusions

Our results show that markers of higher insulin resistance are consistently associated with reduced glycaemic response to DPP4 inhibitor therapy. In our UK-representative cohort 22% of people were obese with high triglycerides (≥2.3mmol/L) and these people had both markedly reduced short-term glycaemic response and shorter durability of response on DPP4 inhibitor treatment. With GLP-1 receptor agonists we found no evidence of an association between markers of insulin response and either 6 month glycaemic response or durability of response to 3 years. Findings were robustly demonstrated in a prospective study and validated in real-world data and provide a starting point for the application of a precision diabetes approach with DPP4 inhibitor therapy.

Strengths of this study include that we have shown consistent findings across several clinical features and markers of insulin resistance in a prospective study and large dataset of electronic healthcare records. We have shown findings are robust with adjustment for baseline HbA_{1c} (12, 23), and potential confounders, and by definition of glycaemic response, with similar associations for short term (6 and 12 month) and long term (3 year durability) glycaemic outcomes**.** We evaluated only adherent individuals (≥75% self-reported adherence) in PRIBA but results were consistent in CPRD where non-adherent individuals were not excluded. Our study is the first to identify characteristics associated with durability of response to DPP4 inhibitor therapy, an area where evidence is limited (24).

Limitations of this study include that we were only able to partially replicate our results from the PRIBA study cohort, as measures such as C-peptide were not available in our replication dataset. Our effect size for triglycerides is notably

smaller in our replication dataset. It is possible this relates to differences in triglyceride measurement (we were unable to confirm if measured triglycerides were fasted in these real-world data) or to increased error in electronic healthcare records in comparison to the prospective study (25), or to the effect of statistical chance in the smaller dataset. The observational analysis precludes causal inference, and in particular measured or unmeasured baseline differences between people are a potential explanation for results in the routine data. The only long-term follow-up data we had to evaluate durability of glycaemic response was from the routine primary care dataset CPRD, further evaluation in a trial setting with greater follow-up than PRIBA would be of considerable interest. An additional important limitation is that this study has examined response to only two of the available therapies. Evidence is limited for other therapies, although a previous study found no evidence of a relationship between clinical insulin resistance or dyslipidaemia markers and glycaemic response with the SGLT-2 inhibitor dapaglifozin (26). High BMI and triglycerides have both been shown to be associated with modest increases in the rate of diabetes progression (27). While this is unlikely to be relevant to our finding for 6 month glycaemic response this could influence our findings for treatment durability, and replication looking at other comparison therapies is therefore particularly important in this context. While we have only examined relatively crude measures of insulin resistance, for clinical practice we consider it very unlikely that more complex measures would ever be feasible (28).

Existing studies of the association between insulin resistance and short-term glycaemic response to DPP4 inhibitors have not shown consistent findings and are constrained by methodological and reporting limitations, as recently reviewed by Bihan and colleagues (12). Meta-regression of study level data

have suggested reduced glycaemic response in people with higher BMI in one study (29), but no relationship in another analysis (30). These studies should be interpreted with some caution due to risk of ecological bias (31, 32). A number of individual clinical trials of DPP4 inhibitors have commented on consistency of glucose response across subgroups defined by baseline BMI or insulin resistance, reduced glycaemic response with high HOMA measured insulin resistance was reported in 2 of 7 studies, and reduced response with high BMI in 6 of 36 studies, as reviewed in Bihan et al (12). No studies reported an opposite direction of effect. These reports are very limited, with the vast majority providing no statistical comparison or details of what analysis was undertaken. An important issue for analysis of this nature is accounting for the influence of baseline HbA_{1c}, the strongest predictor of glycaemic response, which may confound true associations, especially as baseline HbA_{1c} and insulin resistance are positively correlated (23, 33, 34). There are limited data examining the relationship between triglycerides and response to DPP4 inhibitors, however one study stratified people by baseline triglycerides (</>1.7mmol/l) and found the odds of achieving an HbA_{1c} target of 53mmol/mol (7%) were doubled in the low triglyceride subgroup (OR 2.2 [95% CI 1.0-4.7], p=0.04) (35).

While it is plausible our finding of reduced glycaemic response in those with high BMI or high triglycerides directly relates to insulin resistance through reduced effect of drug potentiated insulin secretion, this effect is not apparent in other drugs with effects on insulin secretion, for example previous studies have observed no association between obesity and response to sulfonylurea therapy or GLP-1 receptor agonists (14, 36). An alternative explanation would be a direct effect of lipotoxicity, or indirect associations with other (unmeasured)

factors important to DPP4 inhibitor response. A direct mechanism for lipotoxicity in reducing response to incretin based therapy has been previously suggested, with expression of GLP1 receptors diminished in islets exposed to elevated fatty acid levels in animal models, and beta cell response to GLP1 restored following fatty acid reduction with fibrate pharmacotherapy, however this mechanism would not explain the lack of an association between these features and GLP-1 Receptor Agonist response(37). It has also been shown that GLP-1 response is blunted in obese insulin resistant individuals with high liver fat and also blunted in individuals with high fasting triglycerides (38, 39), therefore impaired GLP-1 secretion in obese insulin resistant individuals represents a potential indirect mechanism that could also account for the lack of a similar relationship for injected GLP-1 receptor agonist therapy. While the lack of association for HDL-c may be considered unexpected, we note HDL-c has a much weaker relationship with insulin resistance than either triglycerides or fasting insulin/C-peptide, which may explain this finding (17).

Our findings have potential implications for clinical practice, as both BMI and triglycerides are routinely available at no additional cost. Stratification of treatment based on these criteria may therefore be cost effective even with the more modest differences in treatment effect seen in our replication cohort. Although our own and previous research suggests these findings may be specific to DPP4 inhibitors further work examining the relationship between these, and other, factors and response to comparator drugs is needed. Our study design, emphasising the importance of replication across datasets, provides an exemplar for such future analyses. In addition while simple categorisation by subgroup may provide a starting point for prediction of therapy response in type 2 diabetes, we anticipate a more sophisticated precision

diabetes approach combining continuous clinical features into a multivariable response calculator will have greatest clinical utility, and this this is an important area for future research (8, 40).

In conclusion, our study shows simple markers of higher insulin resistance are consistently associated with reduced glycaemic response to DPP4 inhibitor therapy. This finding was robustly demonstrated in a prospective study and validated in real-world data and provide a starting point for the application of a precision diabetes approach to DPP4 inhibitor therapy in type 2 diabetes.

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Supplementary Material

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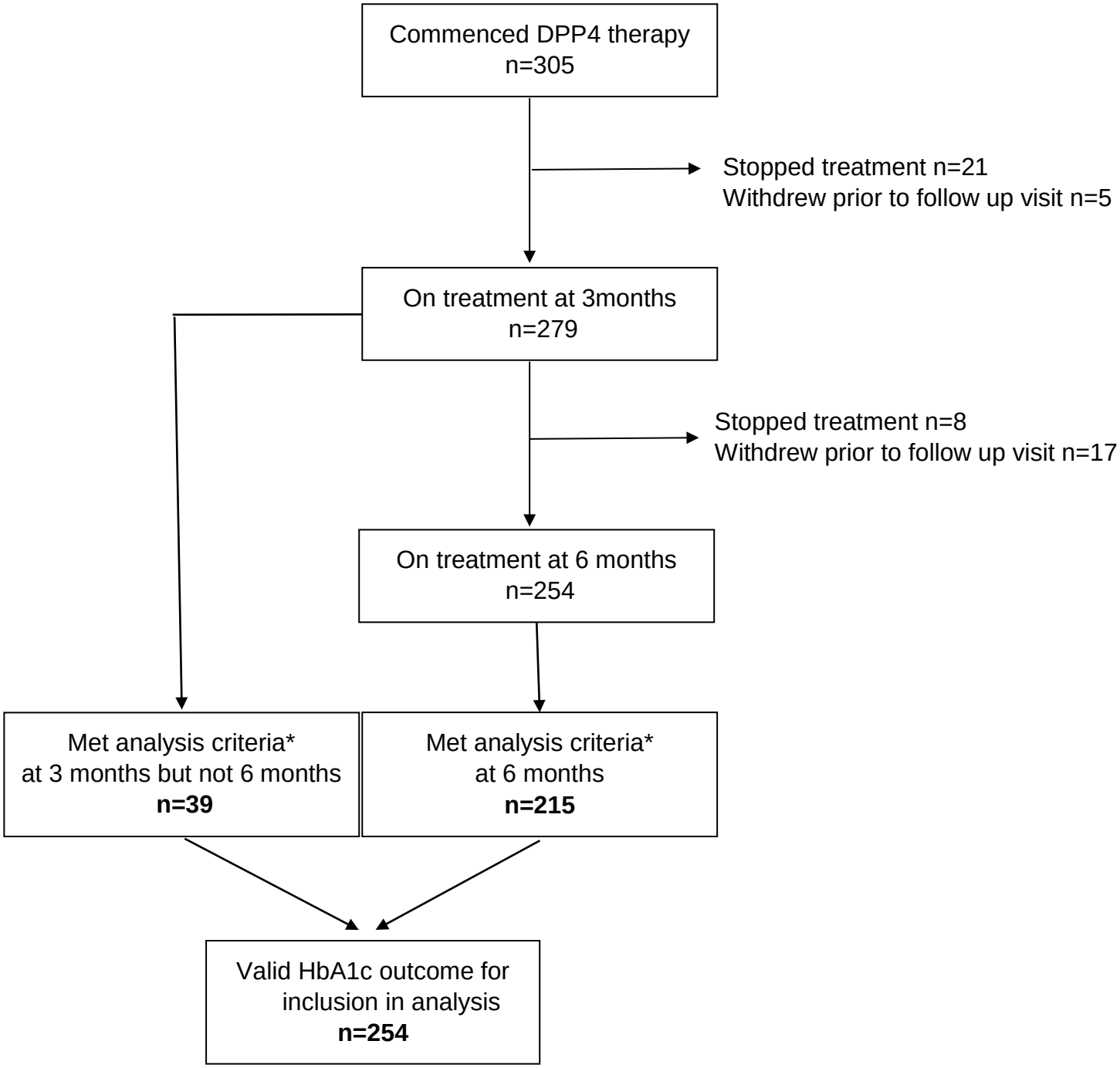
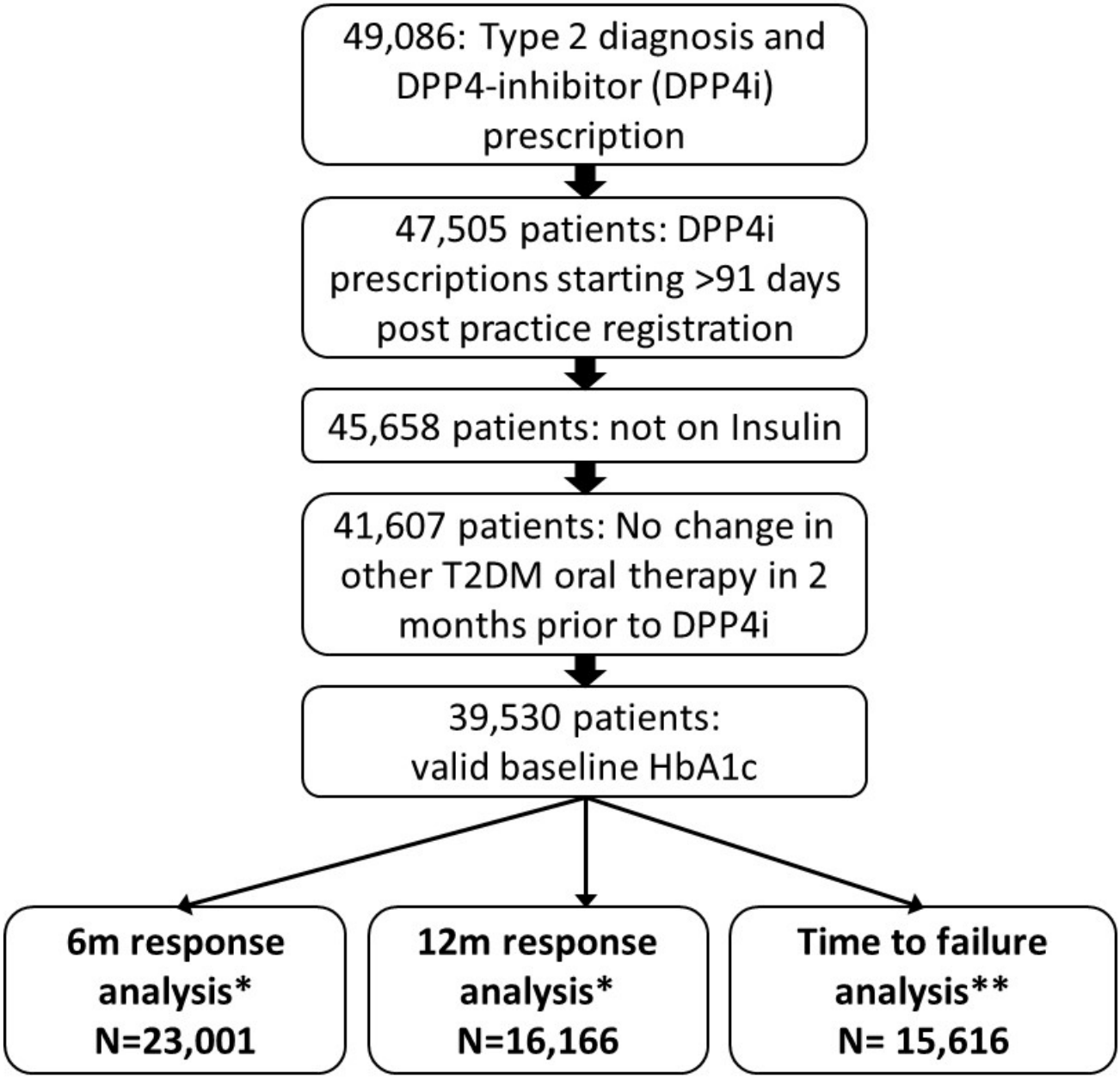
Supplementary figure 1a: PRIBA study Profile



***Analysis inclusion criteria**: no additional of non DPP4 glucose lowering therapy, or discontinuation of >1 co-therapy, between baseline and follow up HbA1c. Self-reported DPP4 adherence (over 2 weeks prior to HbA1c) ≥75%. Participant not receiving insulin treatment at study baseline.

Supplementary Figure 1b: CPRD study profile



*No change in co-therapy over period of interest

**Additional inclusion criteria: baseline HbA1c 7-11%, remained on DPP4i therapy for at least 3m

Supplementary table 1: Associations between markers of insulin resistance and HbA1c response after 6 months, overall (Data table for Figure 1) and stratified by sex in a) PRIBA and b) CPRD. Beta coefficients represent the change in HbA1c per standard deviation higher predictor level, a positive coefficient represents an association with reduced response.

a) PRIBA

	All participants			Males (64%)		Females (36%)	
	Number with valid baseline data	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI)	p-value
HOMA-IR*	242	2.17 (0.62 to 3.72)	0.01	1.69 (-0.26 to 3.64)	0.09	2.87 (0.22 to 5.52)	0.03
Fasting C-peptide	251	1.67 (0.17 to 3.17)	0.03	1.44 (-0.49 to 3.36)	0.14	1.91 (-0.56 to 4.39)	0.13
UCPCR**	203	1.65 (-0.07 to 3.37)	0.06	3.35 (1.05 to 5.65)	<0.01	-0.56 (-3.16 to 2.04)	0.67
Fasting Triglycerides	240	2.54 (0.99 to 4.08)	<0.01	2.20 (0.35 to 4.05)	0.02	3.31 (0.33 to 6.29)	0.03
BMI	254	0.96 (-0.54 to 2.46)	0.21	1.23 (-0.89 to 3.35)	0.25	0.29 (-1.98 to 2.56)	0.80
HDL	243	0.20 (-1.36 to 1.75)	0.81	0.56 (-1.1 to 2.62)	0.60	-0.95 (-3.60 to 1.70)	0.48
SHBG***	214	-1.19 (-2.81 to 0.42)	0.15	-1.19 (-3.35 to 0.97)	0.28	-1.23 (-3.79 to 1.33)	0.34

* HOMA2 measured insulin resistance **UCPCR = post meal urine C-peptide Creatinine ratio; ***SHBG = sex-hormone binding globulin

b) CPRD

	All patients			Males (61%)		Females (39%)	
	Number with valid baseline data	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI)	p-value
BMI	19,430	0.96 (0.78 to 1.15)	<0.01	1.04 (0.78 to 1.30)	<0.01	0.78 (0.51 to 1.05)	<0.01
Triglycerides	15,404	0.72 (0.50 to 0.93)	<0.01	0.82 (0.56 to 1.09)	<0.01	0.57 (0.21 to 0.95)	<0.01
HDL	17,058	-0.08 (-0.28 to 0.13)	0.46	-0.22 (-0.49 to 0.05)	0.11	-0.21 (-0.55 to 0.13)	0.22

Supplementary table 2: Effect sizes for insulin resistance markers controlling for routine clinical characteristics (baseline HBA1c, age at therapy, sex, duration of diabetes, eGFR, ethnicity (CPRD only: white, non-white, missing) and co-therapy change (PRIBA only, CPRD patients all on unchanged therapy). Beta coefficients represent the change in HbA1c at 6 months per standard deviation increase in the predictor, a positive coefficient represents an association with reduced response.

a) PRIBA

	Number of patients	Beta coefficient (95% CI)	p-value
HOMA-IR	205	2.57 (0.73 to 4.40)	<0.01
Fasting C-peptide	212	2.13 (0.33 to 3.94)	0.02
Fasting Triglycerides	215	2.34 (0.44 to 4.25)	0.02
BMI	215	0.67 (-1.15 to 2.50)	0.47
HDL-c	215	0.09 (-1.69 to 1.86)	0.92
SHBG	185	-1.04 (-3.00 to 0.91)	0.29

b) CPRD

	Number of patients	Beta coefficient (95% CI)	p-value
Triglycerides	13,089	0.67 (0.41 to 0.94)	<0.01
BMI	11,683	0.87 (0.61 to 1.12)	<0.01
HDL-c	13,187	-0.11 (-0.35 to 0.14)	0.40

Supplementary table 3: Associations between triglycerides and BMI and HbA1c response after 6 months adjusted for baseline HbA1c, fasting glucose and co-therapy change in PRIBA. Beta coefficients represent the change in HbA1c at 6 months per standard deviation increase in the predictor, a positive coefficient represents an association with reduced response.

	Number of patients	Beta coefficient (95% CI)	p-value
HOMA-IR*	242	1.76 (0.15 to 3.38)	0.03
Fasting C-peptide	242	1.71 (0.21 to 3.21)	0.03
UCPCR**	195	1.50 (-0.22 to 3.21)	0.09
Fasting Triglycerides	231	2.39 (0.84 to 3.94)	<0.01
BMI	244	1.10 (-0.41 to 2.61)	0.15
HDL-c	233	0.20 (-1.36 to 1.76)	0.80
SHBG***	206	-0.90 (-2.53 to 0.73)	0.28

* HOMA2 measured insulin resistance **UCPCR = post meal urine C-peptide Creatinine ratio;
***SHBG = sex-hormone binding globulin

Supplementary table 4: Associations between routine markers of insulin resistance and HbA1c response after 12 months in CPRD. For each predictor we ran a separate linear regression model, adjusted for baseline HbA1c. Beta coefficients represent the change in HbA1c at 12 months per standard deviation increase in the predictor, a positive coefficient represents an association with reduced response.

	Number of patients	Beta coefficient (95% CI)	p-value
Triglycerides	13,942	0.70 (0.45 to 0.96)	<0.01
BMI	11,206	0.81 (0.59 to 1.04)	<0.01
HDL-c	12,273	-0.32 (-0.57 to -0.08)	0.01

Supplementary table 5: Associations between triglycerides and BMI and HbA1c response after 6 months in a combined model adjusted for baseline HbA1c, and (PRIBA only) co-therapy change in a) PRIBA and b) CPRD. Beta coefficients represent the change in HbA1c at 6 months per standard deviation increase in the predictor, a positive coefficient represents an association with reduced response.

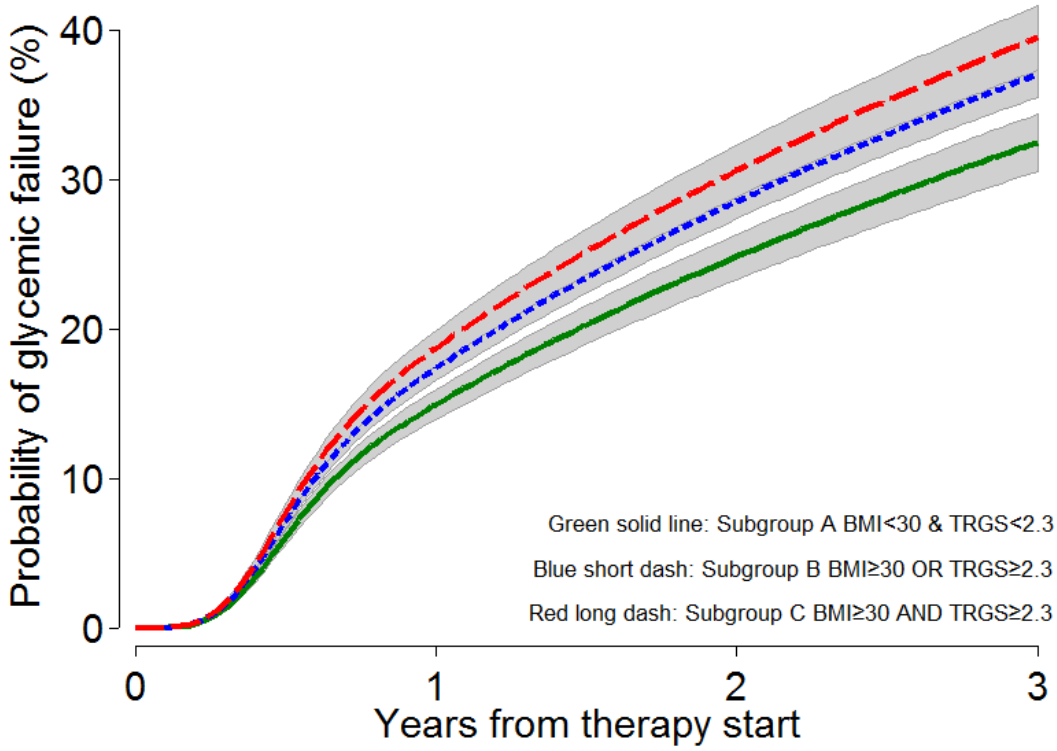
	a) PRIBA (n=240)		b) CPRD (n=13,543)	
	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI)	p-value
Triglycerides	2.33 (0.71 to 3.94)	<0.01	0.56 (0.32 to 0.79)	<0.01
BMI	0.44 (-1.17 to 2.04)	0.59	0.96 (0.73 to 1.18)	<0.01

Supplementary table 6: CPRD hazard ratios for time to glycaemic failure (confirmed HbA1c ≥69 mmol/mol (8.5%)) for each predictor in the multivariable survival model (n=15,616)

	Hazard ratio	95% CI	p-value
BMI & Triglyceride subgroup			
BMI<30 & TRGS<2.3	1 (reference)		
BMI≥30 OR TRGS≥2.3	1.17	1.08-1.27	<0.001
BMI≥30 & TRGS≥2.3	1.28	1.16-1.41	<0.001
Clinical characteristics			
Baseline HbA1c (mmol/mol)*	1.061	1.058-1.064	<0.001
Age at therapy start (year)*	0.990	0.986-0.994	<0.001
Duration of diabetes (year)*	1.004	0.997-1.011	0.29
Female vs male sex	1.075	0.999-1.152	0.04
eGFR (ml/min/1.3m^2)*	1.001	0.999-1.002	0.49

*For continuous variables the hazard ratio represents the change in hazard ratio for a 1 unit increase in the predictor. A hazard ratio > 1 indicates a higher value of that variable is associated with shorter durability of glycaemic response

Supplementary Figure 2: Probability of glycaemic failure (confirmed HbA1c ≥8.5%) over 3 years in CPRD in subgroups defined by the presence or absence of obesity (BMI>=30 kg/m^2) and high triglycerides (TRGs >=2.3mmol/L) - *Subgroup A*: non-obese and normal triglycerides, *Subgroup B*: non-obese OR normal triglycerides, *Subgroup C*: obese and high triglycerides).



Supplementary table 7: CPRD hazard ratios by BMI & Triglyceride subgroup for time to glycaemic failure defined as

a) Confirmed HbA1c ≥53 (7.5%) (n=15,616)*

	Hazard ratio	95% CI	p-value
BMI & Triglyceride subgroup			
BMI<30 & TRGS<2.3	1 (reference)		
BMI≥30 OR TRGS≥2.3	1.08	1.02-1.14	0.01
BMI≥30 & TRGS≥2.3	1.17	1.09-1.25	<0.001

b) Confirmed return to baseline HbA1c level specific to each patient (n=15,616)*

	Hazard ratio	95% CI	p-value
BMI & Triglyceride subgroup			
BMI<30 & TRGS<2.3	1 (reference)		
BMI≥30 OR TRGS≥2.3	1.14	1.05-1.24	0.002
BMI≥30 & TRGS≥2.3	1.29	1.16-1.42	<0.001

*****adjusted for baseline HbA1c, age at therapy, duration of diabetes, sex and eGFR

GLP-1 receptor agonist comparison analysis

Supplementary table 8: GLP-1 receptor agonists - subject baseline characteristics

	PRIBA (n=339)	CPRD (n=4,464)
Characteristics mean (SD) unless stated		
Baseline HbA1c (mmol/mol)	83 (18)	79 (17)
Baseline HbA1c (%)	9.7 (1.7)	9.4 (1.6)
Age at therapy start (years)	55 (10)	59 (9)
Age at diagnosis (years)	47 (10)	51 (8)
Male sex (%)	56%	58%
Duration of diabetes (years)	8 (5)	8 (5)
BMI - median (IQR); mean(SD)	38 (35-44); 40 (8)	37 (34-42); 38 (7)
Ethnicity (%)		
White	95%	46%
Non-White	5%	3%
Missing	0%	51%
Biomarkers median (IQR); mean (SD) unless stated		
*=log-transformed		
Triglycerides (mmol/L)	1.9 (1.4-2.6); 2 (1.1)*	2.0 (1.4-2.8); 2.0 (0.5)*
HDL-c (mmol/L)	1.1 (0.9-1.2); 1.1 (0.3)*	1.1 (0.9-1.2); 1.1 (0.2)*
LDL-c (mmol/L)	2.2 (1.8-2.8); 2.2 (0.8)*	2.0 (1.6-2.6); 2.0 (0.4)*
SHBG (nmol/L)	23 (17-36); 24 (14)*	NA
Fasting C-peptide (pmol/L)	1310 (962-1700); 1255 (594)*	NA
HOMA2-%B	49 (32-75); 48 (29)*	NA
HOMA2 IR	4.1 (3.0-5.3); 4.0 (2.1)*	NA
UCPCR nmol/mmol	3.5 (1.9-6.0); 3.1 (2.8)*	NA
eGFR (ml/min/1.3m^2)	92 (77-111); 95 (27)	88 (74-102); 88 (22)
GAD or IA2 positive (%)	1%	NA
Therapy		
Number of concomitant therapies at therapy start (% of total)		
0	1%	2%
1	26%	36%
2	51%	54%
3+	22%	8%
GLP-1 type (% of total)		
Dulaglutide	0%	1%
Exenatide	40%	44%
Liraglutide	60%	50%
Lixisenatide	0%	6%

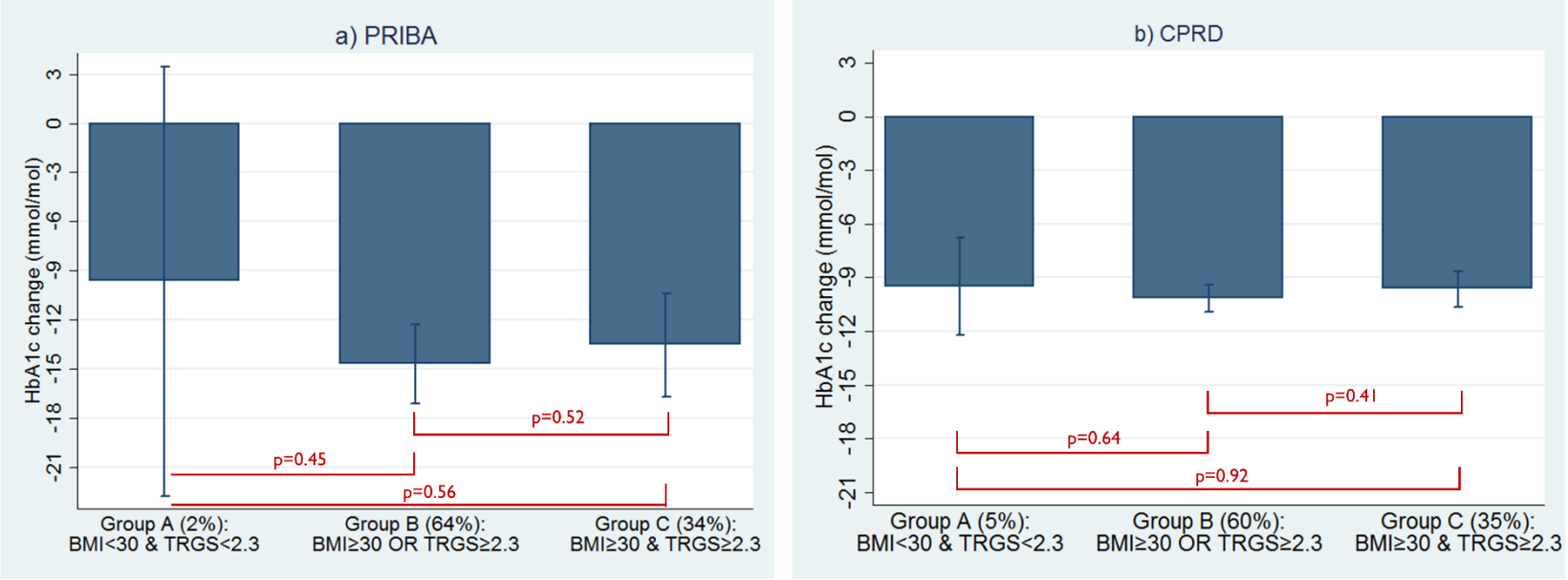
Supplementary table 9: GLP-1 receptor agonists - Associations between markers of insulin resistance and HbA1c response after 6 months, overall (Data table for Supplementary Figure 2) in a) PRIBA and b) CPRD. Beta coefficients represent the change in HbA1c per standard deviation higher predictor level, a positive coefficient represents an association with reduced response.

	PRIBA			CPRD		
	Number with valid baseline data	**Beta coefficient (95% CI)**	**p-value**	**Number with valid baseline data**	**Beta coefficient (95% CI)**	**p-value**
HOMA-IR*	300	0.73 (-0.99 to 2.44)	0.41	NA	NA	NA
Fasting C-peptide	333	0.24 (-1.38 to 1.85)	0.78	NA	NA	NA
UCPCR**	245	0.45 (-1.37 to 2.26)	0.63	NA	NA	NA
Triglycerides	316	0.07 (-1.59 to 1.73)	0.93	2,848	-0.07 (-0.65 to 0.49)	0.80
BMI	337	0.11 (-1.49 to 1.70)	0.90	4,016	-0.19 (-0.66 to 0.28)	0.43
HDL	315	1.08 (-0.55 to 2.71)	0.19	3,126	0.01 (-0.53 to 0.55)	0.97
SHBG***	317	0.56 (-1.09 to 2.21)	0.50	NA	NA	NA

Supplementary table 10: Mean (95% CI) 6 month baseline HbA_{1c} standardised glycaemic response (mmol/mol) for DPP4 inhibitors and GLP receptor agonists in PRIBA and CPRD. Baseline HbA1c is standardised to the mean PRIBA baseline level of 74mmol/mol (8.9%) for all subgroups.

	DPP4 inhibitors		GLP-1 receptor agonists	
BMI & Triglyceride subgroup	**PRIBA**	**CPRD**	**PRIBA**	**CPRD**
BMI<30 & TRGS<2.3	-11.26 (-14.1 to -8.43)	-10.28 (-10.72 to -9.85)	-9.64 (-22.75 to 3.48)	-9.49 (-12.2 to -6.78)
BMI≥30 OR TRGS≥2.3	-9.94 (-12.24 to -7.64)	-8.79 (-9.12 to -8.47)	-14.7 (-17.11 to -12.29)	-10.16 (-10.91 to -9.4)
BMI≥30 & TRGS≥2.3	-5.23 (-8.62 to -1.84)	-7.47 (-7.95 to -6.99)	-13.54 (-16.69 to -10.39)	-9.64 (-10.65 to -8.63)

Supplementary Figure 3: GLP-1 receptor agonists - predicted mean absolute HbA1c change from baseline at 6 months in a) PRIBA b) CPRD across subgroups defined by the presence or absence of obesity (BMI>=30 kg/m²) and high triglycerides (TRGs >=2.3mmol/L) - *Subgroup A*: non-obese and normal triglycerides, *Subgroup B*: non-obese OR normal triglycerides, *Subgroup C*: obese and high triglycerides. Baseline HbA1c is standardised to the mean PRIBA baseline level of 74mmol/mol (8.9%) for all subgroups. Error bars denote 95% confidence intervals.



Supplementary table 11: GLP-1 receptor agonists - CPRD hazard ratios for time to glycaemic failure (confirmed HbA1c ≥69 mmol/mol (8.5%) for each predictor in the multivariable survival model (n=2,795)

	Hazard ratio	95% CI	p-value
BMI*	1.01	1.00-1.02	0.29
Triglycerides*	0.99	0.95-1.04	0.80
Baseline HbA1c (mmol/mol)*	1.05	1.04-1.06	<0.001
Age at therapy start (year)*	0.98	0.97-0.99	<0.001
Duration of diabetes (year)*	1.01	0.99-1.03	0.21
Female vs male sex	0.78	0.67-0.91	0.001
eGFR (ml/min/1.3m^2)*	1.00	1.00-1.00	0.63

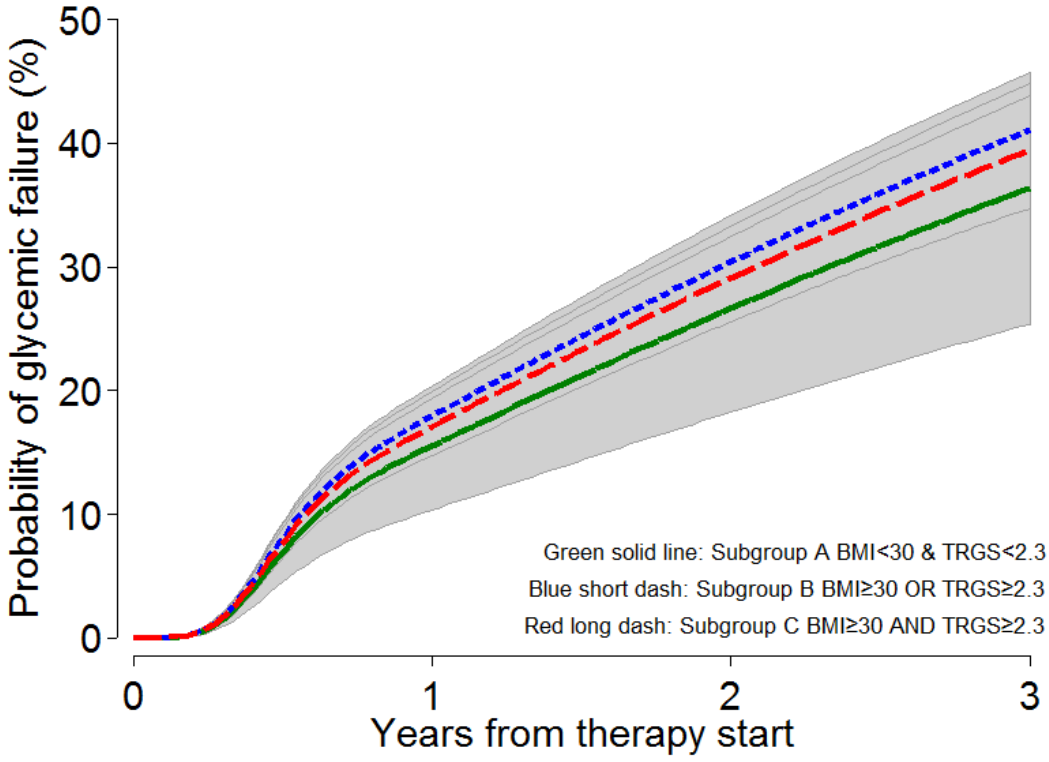
*For continuous variables the hazard ratio represents the change in hazard ratio for a 1 unit increase in the predictor. A hazard ratio > 1 indicates a higher value of that variable is associated with shorter durability of glycaemic response

Supplementary table 12: GLP-1 receptor agonists - CPRD hazard ratios for time to glycaemic failure (confirmed HbA1c ≥69 mmol/mol (8.5%)) for each predictor in the multivariable survival model (n=2,795)

	Hazard ratio	95% CI	p-value
BMI & Triglyceride subgroup			
BMI<30 & TRGS<2.3	1 (reference)		
BMI≥30 OR TRGS≥2.3	1.21	0.85-1.73	0.29
BMI≥30 & TRGS≥2.3	1.13	0.79-1.63	0.50
Clinical characteristics			
Baseline HbA1c (mmol/mol)*	1.05	1.04-1.06	<0.001
Age at therapy start (year)*	0.98	0.97-0.99	<0.001
Duration of diabetes (year)*	1.01	0.99-1.03	0.22
Female vs male sex	0.79	0.68-0.92	0.002
eGFR (ml/min/1.3m^2)*	1.00	1.00-1.00	0.60

*For continuous variables the hazard ratio represents the change in hazard ratio for a 1 unit increase in the predictor. A hazard ratio > 1 indicates a higher value of that variable is associated with shorter durability of glycaemic response

Supplementary Figure 4: GLP-1 receptor agonists - Probability of glycaemic failure (confirmed HbA1c ≥8.5%) over 3 years in CPRD in subgroups defined by the presence or absence of obesity (BMI>=30 kg/m^2) and high triglycerides (TRGs >=2.3mmol/L) - *Subgroup A*: non-obese and normal triglycerides, *Subgroup B*: non-obese OR normal triglycerides, *Subgroup C*: obese and high triglycerides).



Chapter 4

Sex and BMI alter the benefits and risks of sulfonylureas and thiazolidinediones in type 2 diabetes: A framework for evaluating stratification using routine clinical and individual trial data

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Acknowledgments of co-authors and contributions to paper

Andrew Hattersley, Ewan Pearson, Beverley Shields, Angus Jones, Salim Janmohamed, William T Hamilton and I designed the study. Beverley Shields, Lauren Rodgers and Michael Weedon extracted the CPRD data. Beverley Shields analysed the CPRD data, Mike Lonergan prepared and analysed the GoDARTs data, I prepared and analysed the trial data. I drafted the manuscript, with assistance from Beverley Shields and Andrew Hattersley. All authors provided support for the interpretation of results, critically revised the manuscript, and approved the final draft of the manuscript.

Abstract

Objective

The choice of therapy for type 2 diabetes after metformin is guided by overall estimates of glycemic response and side-effects seen in large cohorts. A stratified approach to therapy would aim to improve on this by identifying subgroups of people whose glycaemic response or risk of side-effects differ markedly. We assessed if simple clinical characteristics could identify people with differing glycemic response and side-effects with sulfonylureas and thiazolidinediones.

Research design and methods

We studied 22,379 individuals starting sulfonylurea or thiazolidinedione therapy in U.K. Clinical Practice Research Datalink (CPRD) to identify features associated with increased one-year HbA_{1c} fall with one therapy class and reduced with the second. We then assessed if pre-specified subgroups defined by the differential clinical factors showed differing five-year glycemic response and side-effects with sulfonylureas and thiazolidinediones using individual randomised trial data from ADOPT (first-line therapy, n=2,725) and RECORD (second-line therapy, n=2,222). Further replication was conducted using routine clinical data from the GoDARTS (n=1,977).

Results

In CPRD male sex and lower BMI were associated with greater glycemic response with sulfonylureas and a lesser response with thiazolidinediones (both $p<0.001$). In ADOPT and RECORD non-obese males had a greater overall HbA_{1c} reduction with sulfonylureas than thiazolidinediones ($p<0.001$); in contrast obese females had a greater HbA_{1c} reduction with thiazolidinediones

than sulfonylureas ($p<0.001$). Weight gain and oedema risk with thiazolidinediones were greatest in obese females however hypoglycaemia risk with sulfonylureas was similar across all subgroups.

Conclusions

Subgroups defined by sex and BMI have a different pattern of benefits and risks on thiazolidinedione and sulfonylurea therapy. Subgroup specific estimates can inform discussion about the choice of therapy after metformin for an individuals. Our approach using routine and shared trial data provides a framework for future stratification research in type 2 diabetes.

Introduction

In type 2 diabetes there is limited guidance to help clinicians and patients choose between the different glucose-lowering therapy options recommended after metformin.(1-3) Guidelines suggest a discussion of the benefits, adverse effects, and costs of therapy to select the most appropriate medication for a particular patient.(1) Estimates of important clinical outcomes such as HbA_{1c}, weight change and risk of side-effects are at present derived from whole trial populations and a key question is whether they vary across patient subgroups defined by simple characteristics.(1) If estimates do vary by simple characteristics this may provide a starting point for a stratified approach in type 2 diabetes; the 'targeting of treatments according to the biological or risk characteristics shared by patients'.(4)

Sulfonylureas and thiazolidinediones are recommended second and third line therapy options in all major type 2 diabetes guidelines.(1, 2) They represented 50% of new second line prescriptions in 2016 in the U.S (sulfonylureas 46%, thiazolidinediones 4%).(5) As the only generic oral agents they are over 10-fold cheaper than the common alternatives DPP4 inhibitors and SGLT2 inhibitors.(1, 6) Glycemic response, weight change and common side effects have been well described in whole trial populations for both therapies.(7-11) Differences in glycemic response by sex and BMI with thiazolidinediones and sulfonylureas have been previously suggested in observational studies,(12, 13) but no study has systematically compared whether the benefits and risks of these therapies vary across subgroups defined by simple clinical patient characteristics.

Sulfonylureas and thiazolidinediones have, in contrast to newer therapies, been evaluated head-to-head in two long-term, randomized trials, ADOPT and RECORD.(7, 14) ADOPT showed there was a greater durability of response up

to 5 years with the thiazolidinedione rosiglitazone compared to either the sulfonylurea glyburide or metformin.(7)The full individual participant data of both trials are now available through Clinical Study Data Request,(15) and a current topic of debate is how to improve the output of secondary research projects using such shared trial datasets.(16) In this study we present a practical and cost-effective framework for stratification research using shared trial datasets alongside routine clinical data. We applied this framework to systematically evaluate whether simple clinical patient characteristics can be used to stratify therapy with sulfonylureas and thiazolidinediones.

Research Design and Methods

Framework for stratification research

In discovery analysis we explored routine clinical data to identify simple characteristics associated with glycemic response to sulfonylureas and thiazolidinediones, and used the results to define subgroups likely to show differential response. In validation analysis we evaluated differences in response within subgroups as a pre-specified hypothesis in ADOPT and RECORD, the two largest head-to-head randomized trials of sulfonylureas and thiazolidinediones available via Clinical Study Data Request.(7, 9, 14, 17, 18) We also evaluated the secondary outcomes of weight change and risk of the common side effects of hypoglycemia, oedema and fracture within each subgroup (see Supplementary Figure 1 for our framework for stratification research using routine clinical and shared trial data).

Datasets

We analysed four datasets. Due to its large sample size, discovery analysis was conducted in routine clinical data from UK Clinical Practice Research Datalink (CPRD), with validation in trial datasets (ADOPT and RECORD) and a further routine clinical dataset (GoDARTs). Scientific approval for the use of CPRD data was granted by the CPRD Independent Scientific Advisory Committee (ISAC 13_177R) and permission to use the GoDARTs data was granted by the East of Scotland Regional Ethics Committee (09/21402/44). Data for both ADOPT and RECORD trials were accessed through the Clinical Trial Data Transparency Portal under approval from GSK (Proposal 930).

CPRD

CPRD is the world's largest database of anonymized primary care electronic health records.(19) Our study protocol for CPRD data ascertainment has been previously reported.(20) We studied 22,379 non-insulin treated people with type 2 diabetes and prescription records for a sulfonylurea or thiazolidinedione from the February 2014 build of CPRD GOLD (see CPRD data supplement for product codes). We included people with a duration of diabetes over one year (to minimise effect of lifestyle change following diagnosis) and at least one year on-therapy without change in co-prescribed glucose lowering therapy (see Supplementary Figure 2 for CPRD patient flow diagram).(20)

Trials

ADOPT and RECORD were prospective type 2 diabetes trials over at least 5 years of, respectively, glycemic durability and cardiovascular outcomes, in participants randomized to thiazolidinedione, sulfonylurea or metformin therapy.(7, 9, 14, 17, 18) In ADOPT we included participants in the intention to

treat population with a valid baseline BMI randomized to sulfonylurea (glibenclamide) or thiazolidinedione (rosiglitazone) therapy (n=2,725). In RECORD we included participants in the intention to treat population on background metformin randomized to sulfonylurea (glibenclamide (18%), gliclazide (30%) or glimepiride (52%) according to local practice) or thiazolidinedione (rosiglitazone) add-on therapy (n=2,222).

Genetics of Diabetes Audit and Research in Tayside Study (GoDARTs)

GoDARTs contains information from the medical records of 18,276 people resident in eastern Scotland. We examined 1,977 individuals with type 2 diabetes and valid prescription records for a sulfonylurea or thiazolidinedione.

Analysis – data extraction and definitions

CPRD – discovery analysis

The primary outcome was one year glycemic response in people starting therapy with a sulfonylurea (any) or thiazolidinedione (pioglitazone or rosiglitazone) for the first time.

We extracted HbA_{1c} at therapy start and at one year to calculate initial HbA_{1c} response (one year HbA_{1c} – baseline HbA_{1c}; see CPRD data supplement for HbA_{1c} codes), and baseline clinical characteristics: sex, BMI, age at diagnosis, duration of diabetes and eGFR.(20) Baseline HbA_{1c} was defined as the closest HbA_{1c} to the drug start date in the 91 days prior to the drug start date. One year HbA_{1c} was defined as the closest HbA_{1c} to one year after drug start date (+/-3 months). HbA_{1c} response was only valid if there were no changes to diabetes medications between 60 days prior to the baseline HbA_{1c} and the date of the one year HbA_{1c}.(20) No adjustment was made for dose. To evaluate the secondary outcomes of long-term response and side effects we extracted

measures of body weight, HbA_{1c}, and records of fracture and oedema (see CPRD data supplement for fracture and oedema codes) over five years from the start of therapy. People with a fracture or oedema record in the two years prior to the drug start date were excluded from fracture and oedema analyses. We defined adherence as a Medication Possession Ratio (the number of days of available medication divided by the number of days between the first and last prescription dates, multiplied by 100). Due to the association between adherence and response,(21) only people issued sufficient prescriptions (medical possession ratio of between 80% and 120%) were included in analysis.

Trials – validation analysis

We used individual participant data from the trials to validate initial findings in CPRD. Based on the CPRD results we pre-specified four subgroups defined by sex and obesity ($BMI \geq 30 kg/m^2$). For each subgroup we compared average glycemic response by therapy over five years as the difference in area under the HbA_{1c} response curve. This is equivalent to the time-updated HbA_{1c} measure used in the UKPDS outcomes model.(22) At years one, three and five we also estimated the difference between therapies in average glycemic response. We assessed annual weight change (percentage change from baseline) using the same approach. We also compared durability of response by therapy as measured by time to therapy failure. Failure was defined as in the original trials (ADOPT: confirmed fasting plasma glucose ≥180 mg/dl; RECORD confirmed HbA_{1c} ≥8.5%). To evaluate side effects over five years we estimated the on-therapy risk of fracture (any), clinically determined peripheral oedema (all events, moderate/severe events (as defined as in the original trials as sufficient to, respectively, interfere with or prevent normal everyday activities)) and

clinically determined hypoglycemia (all, moderate/severe as defined in the original trials).(9, 17) In ADOPT we excluded people with a history of oedema from oedema analysis, in RECORD history of oedema was not available.

GoDARTs

We evaluated average glycemic response by therapy over five years using the same approach used for CPRD.

Statistical Analysis

Short-term response: CPRD

We assessed associations between baseline clinical characteristics (BMI, sex, age at diagnosis, duration of diabetes, eGFR) and one year glycemic response in linear regression models. A series of baseline HbA_{1c}-adjusted models examined each clinical characteristic in turn, separately for each therapy.(23) We conducted a complete case analysis for each variable of interest, including all people with valid data even if they had missing data for other clinical characteristics. Diagnostic plots of residuals were examined to check model assumptions were met. Based on the initial analysis we defined four subgroups defined by sex and obesity (BMI>30 v BMI$\leq$30kg/m^2) and for each therapy calculated baseline HbA_{1c} adjusted least-square mean estimates of one-year response for each subgroup. To test for an overall effect of heterogeneity by sex and obesity subgroup we used a likelihood ratio test to compare a model with a drug:subgroup interaction with a nested model without an interaction term.

Long-term response, weight gain and side effects: trial data

We compared how each outcome was altered by therapy in each subgroup separately. We conducted response and weight change analysis in each trial separately, but pooled the data for side effects to increase study power. To estimate glycemic response over time we fitted baseline adjusted repeated measures mixed effect models using on-therapy HbA_{1c} values at each study visit (n=22 ADOPT, n=19 RECORD) up to five years, including fixed effects for study visit, baseline HbA_{1c}, therapy, visit by therapy interaction and visit by baseline HbA_{1c} interaction, and individual-level random effects with an unstructured covariance matrix. Missing on-therapy HbA_{1c} records were assumed to be missing at random. We calculated point estimates and 95% confidence intervals (CI) for the difference in average glycemic response by therapy at years one, three and five through contrasts of least-squares mean HbA_{1c} change. We tested for an overall effect of heterogeneity by subgroup using the same interaction test as in CPRD. Weight change was modelled using the same approach.

To measure the net difference in HbA_{1c} response between therapies we calculated the cumulative area under the HbA_{1c} response curve (AUC) for each participant at every study visit using the trapezoidal rule. Participant AUC was then used as the outcome in repeated measures mixed effects models of the same structure as for glycemic response. A least-squares mean point estimate (95% CI) was calculated at year five to contrast overall response by therapy.

Time to therapy failure and side effects were estimated using the Kaplan-Meier method and Cox proportional hazards regression. Proportional hazards assumptions were evaluated using Schoenfeld residuals and were satisfied for all analyses. For each side effect the hazard ratio contrasting thiazolidinedione

therapy with sulfonylurea therapy was estimated for each subgroup using an individual participant meta-analysis of data from both trials.

Long-term response, weight gain and side effects: CPRD

In CPRD we replicated analyses using the same models as described above for all outcomes except hypoglycemia. For analysis of long-term HbA_{1c} response, we extracted all HbA_{1c} records between 60 days prior to the drug start date up to five years after the drug start date whilst on unchanged therapy. HbA_{1c} records were categorised to three monthly intervals (nearest HbA_{1c} record +/- 1.5 months) to enable comparison with the trials. Where data points were missing, results were interpolated to ensure each time point reflected the same population. The same approach was used for weight change, but with weights extracted at 6 monthly intervals (+/- 3months). For time to failure analysis, therapy failure was defined as two consecutive HbA_{1c}s ≥8.5% or one HbA_{1c} ≥8.5% followed by the addition of another therapy (the same definition of glycemic failure used in RECORD). Data were censored if prescription records ended before a change in therapy. We excluded people with changes to diabetes therapy without a prior HbA_{1c} ≥8.5% as these changes were unlikely to relate to glycemic failure.

CPRD data extraction was conducted using Stata v13.0. All other analyses were conducted using R.

Results

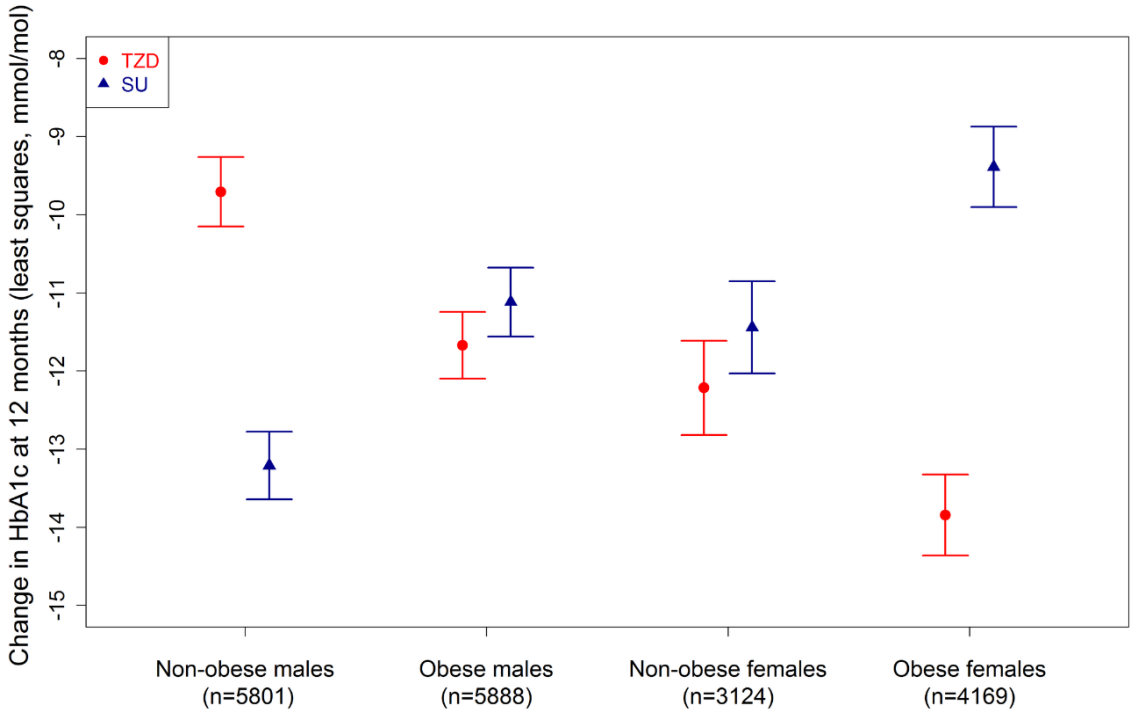
Routine clinical data: sex and obesity are associated with differential glycemic response with sulfonylureas and thiazolidinediones

In CPRD we examined clinical factors associated with one year glycemic response amongst 22,379 eligible individuals (10,960 thiazolidinedione; 11,419 sulfonylurea) (see Supplementary Table 1 for baseline characteristics). Sex and BMI showed the greatest differential response to therapy (Supplementary Figure 3). Compared to males, females had a greater response with thiazolidinediones, but a lesser response with sulfonylureas (both $p<0.001$). Higher BMI was associated with greater response with thiazolidinediones, but a lesser response with sulfonylureas (both $p<0.001$). Older age at diagnosis and lower eGFR were associated with a greater response to both therapies, there was greater response to thiazolidinediones with shorter diabetes duration, and greater response to sulfonylureas with longer diabetes duration and higher HDL (Supplementary Figure 3).

As sex and BMI showed the greatest differential response we specified four subgroups defined by sex and obesity (BMI>30 v BMI$\leq$30kg/m^2) for use in subsequent analysis. We found evidence of heterogeneity of response by subgroup ($p<0.001$). Figure 1 shows one year glycemic response by therapy for the four subgroups. Non-obese males had a greater one year response with sulfonylureas than thiazolidinediones (baseline adjusted change in HbA_{1c}: -13.2 (95% CI -13.6;-12.8) v -9.7 (95% CI -10.1;-9.3) mmol/mol, $p<0.001$), whereas obese females had a greater one year response with thiazolidinediones than sulfonylureas (-13.8 (95% CI -14.3;-13.3) v -9.4 (95% CI -9.9.1;-8.9) mmol/mol, $p<0.001$). Obese males and non-obese females showed similar responses with both therapies (both $p=0.6$). Results were consistent for pioglitazone and

rosiglitazone when analysed separately, and for gliclazide and non-gliclazide sulfonylureas (Supplementary Figure 4).

Figure 1: CPRD: One year glycemic response (baseline adjusted change in HbA_{1c}) with thiazolidinediones (red dots) and sulfonylureas (blue triangles), by sex and obesity defined subgroup. Data are presented as least square means adjusted for baseline HbA_{1c} ± 95% CI. A reduction (improvement) in HbA_{1c} is represented as a negative value.



Trial data: non-obese males have greater glycemic response with sulfonylureas, obese females with thiazolidinediones

We went on to assess if the sex and obesity defined subgroups also showed differential response when randomly allocated to therapy in the ADOPT (n=2,725) and RECORD (n=2,222) trials. Randomisation resulted in well matched individuals for each therapy within each subgroup (see Supplementary Tables 2 and 3 for baseline characteristics). There were marked differences in response with both therapies in the four subgroups with a clear similarity between the two trials (test for heterogeneity in ADOPT and RECORD both $p<0.001$, Figure 2a and 2b). Over five years there was a greater overall glycemic response for non-obese males with sulfonylureas (both trials $p<0.001$),

relating to the greater earlier benefit with sulfonylureas over thiazolidinediones that persisted beyond 2 years in both trials. In contrast there was a greater overall glycemic response for obese females with thiazolidinediones over sulfonylureas (both trials $p<0.001$), and there was little early benefit with sulfonylureas.

Trial data: absolute risk of therapy failure differs markedly by subgroup

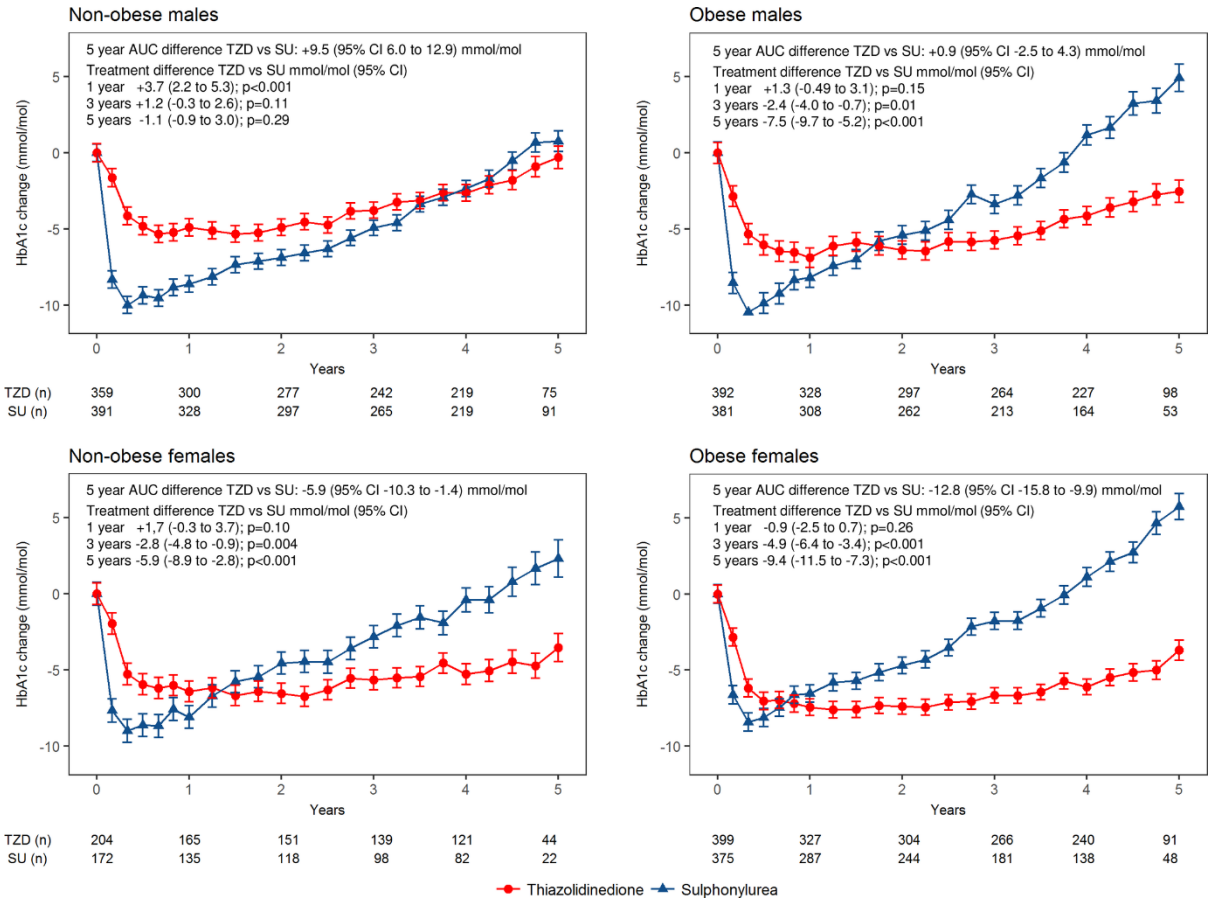
We assessed the risk of monotherapy and dual-therapy failure, respectively, in ADOPT and RECORD. In both trials for non-obese males there was no difference in the five year risk of failure on the two therapies but all other subgroups were less likely to fail with thiazolidinediones than sulfonylureas (Hazard ratios 0.23-0.72, test for heterogeneity ADOPT $p<0.001$, RECORD $p=0.01$, Table 1, Supplementary Figures 5-6). In ADOPT, risk of monotherapy failure at five years with thiazolidinediones was lower for obese females (11%) than non-obese males (22%), whilst with sulfonylureas failure risk was lower for non-obese males (22%) than obese females (42%) (Table 1).

Trial data: increased risk of weight gain and oedema with thiazolidinediones for all subgroups

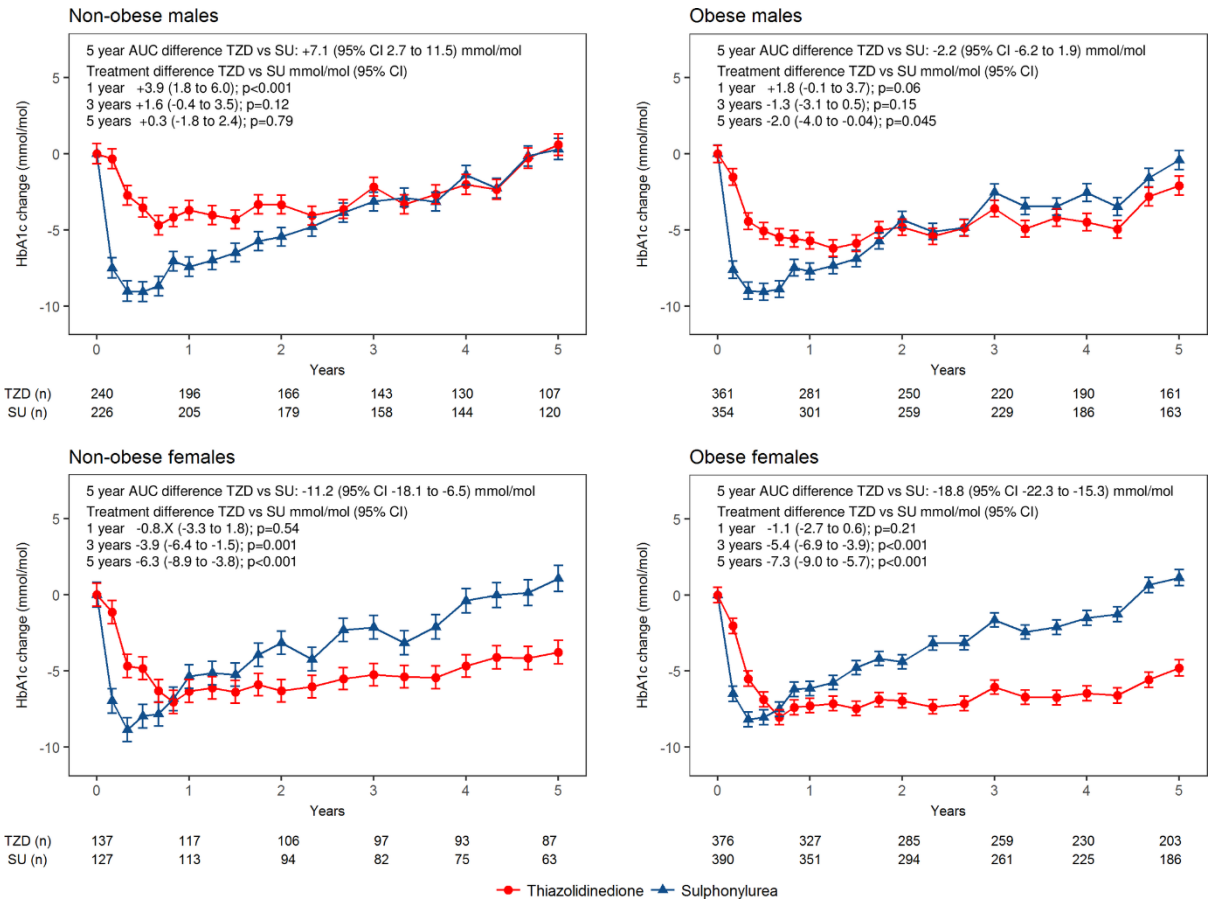
Weight was increased for all subgroups with thiazolidinediones compared to sulfonylureas but this was much more marked in obese females (Figure 2c, Supplementary Figure 7). Oedema was more common with thiazolidinediones compared to sulfonylureas for all subgroups; this resulted in the largest difference in absolute risk for obese females who are most likely to develop oedema regardless of therapy (Table 2, Supplementary Figure 8).

Figure 2: 5 year glycemic response (change from baseline in HbA_{1c}) and weight change (percentage change from baseline) with thiazolidinediones (TZD, red dots) and sulfonylureas (SU, blue triangles), by sex and obesity defined subgroup. Data are presented as means at each study visit ± standard error from mixed effects models. A reduction (improvement) in HbA_{1c} is represented as a negative value. For AUC and treatment difference estimates positive values favour SU, negative values favour TZD. For RECORD weight change data see Supplementary Figure 7.

a) ADOPT trial: absolute glycemic response (mmol/mol)



b) RECORD trial: absolute glycemic response (mmol/mol)



c) ADOPT trial: weight change from baseline (%)

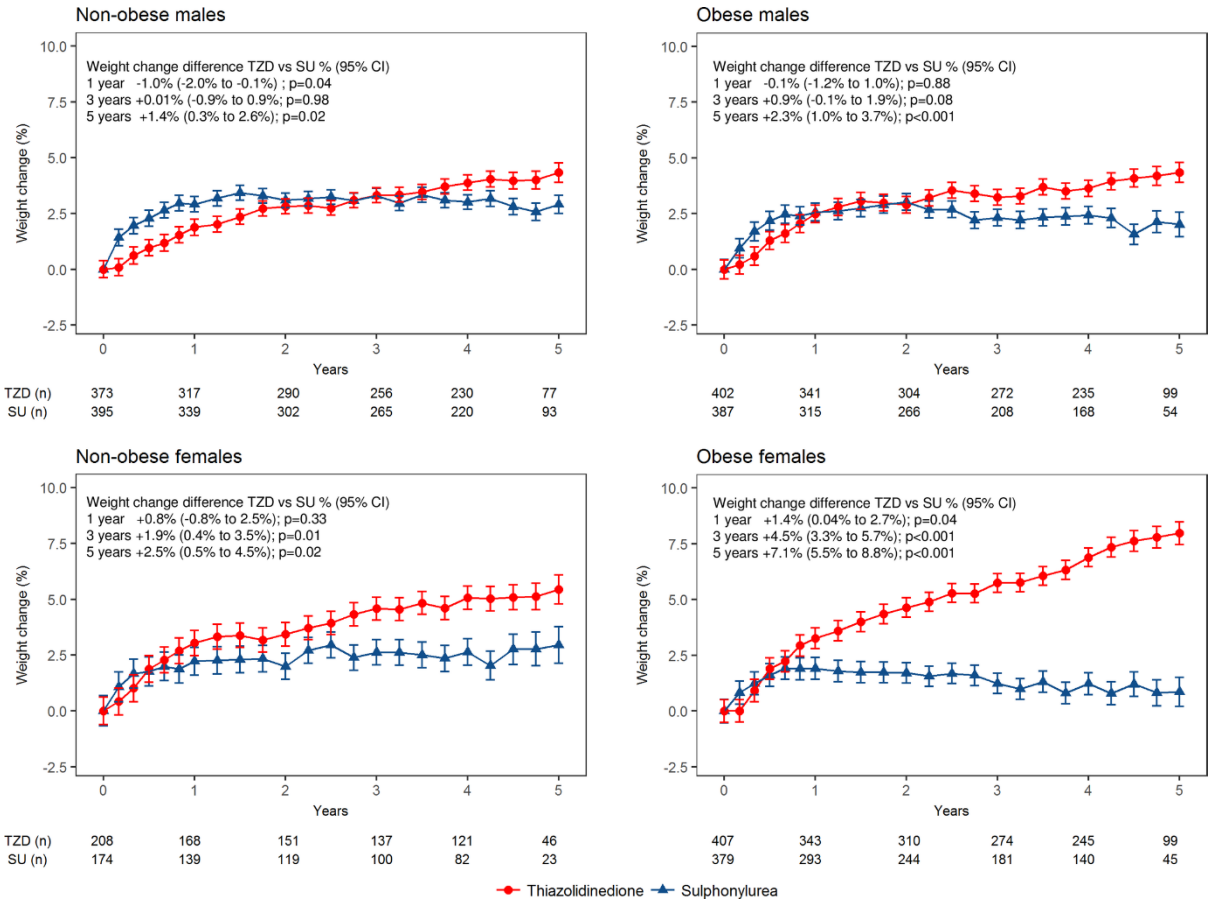


Table 1: Absolute and relative risk of glycemic failure with thiazolidinediones (TZD) and sulfonylureas (SU) in trial data, by sex and obesity defined subgroup. Failure defined according to original trial protocol (ADOPT trial (monotherapy) defined as fasting plasma glucose≥180mg/dl; RECORD (dual therapy with metformin) defined as HbA_{1c}≥8.5%. Relative risks presented as hazard ratios (95% CI) for TZD compared to SU.

ADOPT monotherapy failure	**No. of participants**		**No. of events**		**Absolute 5 year risk (%)**		**Hazard ratio (95% CI) (TZD vs. SU)**	**p value**
	TZD	**SU**	**TZD**	**SU**	**TZD**	**SU**		
Non-obese males	373	395	47	63	21.7%	21.9%	0.78 (0.54-1.14)	0.21
Obese males	402	387	44	108	15.0%	43.8%	0.32 (0.23-0.46)	<0.001
Non-obese females	208	174	16	34	10.9%	31.5%	0.34 (0.19-0.62)	<0.001
Obese females	407	379	31	93	11.6%	42.2%	0.23 (0.16-0.35)	<0.001

RECORD dual-therapy failure	**No. of participants**		**No. of events**		**Absolute 5 year risk (%)**		**Hazard ratio (95% CI) (TZD vs. SU)**	**p value**
	TZD	**SU**	**TZD**	**SU**	**TZD**	**SU**		
Non-obese males	240	228	66	70	33.6%	34.0%	1.00 (0.72-1.40)	0.94
Obese males	361	356	92	132	30.7%	41.4%	0.72 (0.55-0.94)	0.02
Non-obese females	137	127	26	45	20.7%	38.8%	0.52 (0.32-0.84)	0.01
Obese females	379	394	72	142	22.7%	40.5%	0.52 (0.38-0.68)	<0.001

Trial data: increased risk of fracture with thiazolidinediones only for females

Fracture was more common with thiazolidinediones compared to sulfonylureas but only for females. Absolute risk was similar for obese and non-obese females (Table 2, Supplementary Figure 9).

Trial data: increased risk of hypoglycemia with sulfonylureas for all subgroups

Sulfonylureas, compared with thiazolidinediones, increased the risk of moderate/severe hypoglycemia for all subgroups (Table 2, Supplementary Figure 10). Hazard ratios for hypoglycemia of any severity were consistent with those for moderate/severe events (Supplementary Tables 4-5). For all side effects there was a similar differences between therapies when the trials were analysed separately (Supplementary Tables 4-5).

Routine clinical data: results for long-term glycemic response, time to failure and side effects were consistent with trial data

In CPRD and GoDARTs (see Supplementary Table 6 for GoDARTs baseline characteristics), five year glycemic response results were consistent with the trials (Supplementary Figures 11 & 16). In CPRD differences by therapy in time to failure results were similar to the trials although absolute failure rates were higher (Supplementary Figure 12). Weight gain, oedema and fracture results in CPRD were comparable to trial data (Supplementary Figures 13-15).

Summary of results

For subgroup data summaries of glycemic response, weight change and risk of side effects estimates specific to each sex and obesity defined subgroup see the Subgroup data summary (Supplementary material).

Table 2: Absolute and relative risk of side effects over 5 years with thiazolidinediones (TZD) and sulfonylureas (SU) in ADOPT & RECORD combined, by sex and obesity defined subgroup. Relative risks presented as hazard ratios (95% CI) for TZD compared to SU. HRs and p values from meta-analysis of both trials.

Side effect	No. of participants		No. of events		Absolute 5 year risk (%)		Hazard ratio (95% CI) (TZD vs. SU)	p value
	TZD	SU	TZD	SU	TZD	SU		
Non-obese males								
Oedema (Moderate/Severe)	607	620	13	4	3%	1%	3.57 (1.16-10.94)	0.03
Fracture (All)	613	623	26	18	7%	4%	1.59 (0.87-2.89)	0.16
Hypoglycaemia (Moderate/Severe)	613	623	14	90	3%	16%	0.15 (0.09-0.27)	<0.001
Obese males								
Oedema (Moderate/Severe)	740	719	37	16	7%	3%	2.45 (1.34-4.47)	<0.01
Fracture (All)	763	743	30	28	6%	5%	1.02 (0.61-1.71)	0.94
Hypoglycaemia (Moderate/Severe)	763	743	13	70	2%	11%	0.17 (0.09-0.31)	<0.001
Non-obese females								
Oedema (Moderate/Severe)	340	293	13	5	5%	2%	2.10 (0.75-5.89)	0.16
Fracture (All)	345	301	31	8	14%	3%	3.15 (1.45-6.87)	<0.01
Hypoglycaemia (Moderate/Severe)	345	301	10	44	4%	17%	0.17 (0.09-0.35)	<0.001
Obese females								
Oedema (Moderate/Severe)	749	746	60	25	10%	5%	2.16 (1.35-3.45)	<0.01
Fracture (All)	786	773	77	33	14%	6%	2.14 (1.42-3.23)	<0.001
Hypoglycaemia (Moderate/Severe)	786	773	18	83	3%	13%	0.19 (0.11-0.31)	<0.001

Conclusions

Stratification of therapy with sulfonylureas and thiazolidinediones is possible using sex and BMI

We have robustly demonstrated across four datasets that sex and BMI alter the benefits and risks of type 2 diabetes therapy with sulfonylureas and thiazolidinediones. We show in non-obese males the glycemic response with sulfonylureas is better on average in the first 5 years than on thiazolidinediones, without excess weight gain, but with an increased risk of hypoglycemia. For obese females there is a clear glycemic benefit over the first 5 years with thiazolidinediones compared to sulfonylureas, but there is increased weight gain and susceptibility to oedema and fracture. Our findings will allow for much more informed discussion of the benefits and risks of these therapies than the present 'one size fits all' approach (see supplementary Subgroup Data Summary for estimates specific to each sex and obesity defined subgroup).

Our results provide one of the first examples of stratification of therapy in type 2 diabetes based on simple clinical characteristics.(24) A recent data-driven cluster analysis proposed five subgroups of diabetes with differing disease progression and risk of complications, but did not evaluate whether subgroups differed in their response to therapy.(25) To-date successful stratification in other conditions has involved expensive genetic testing, as applied in cancer and single gene diseases such as monogenic diabetes.(26, 27) Expensive testing is unlikely to become practical or justified in type 2 diabetes, a highly prevalent condition with relatively inexpensive therapy. Type 2 diabetes genetic studies have identified polymorphisms associated with drug response but the impact of these, at present, are too small to guide clinical management, in contrast to our results.(28-32)

A framework for stratification research using shared trial data alongside routine clinical data

This study is an early and important demonstration of how shared trial data can be harnessed to meaningfully benefit patients.(16) We propose a novel and cost-effective framework to use shared trial data in stratification research. Our framework can be applied to study other type 2 diabetes therapies and to study stratification in other chronic conditions. It has great potential to improve the output of future studies using shared trial data.

Comparison to previous studies

Whilst no existing studies have systematically assessed whether both the benefits and risks of these two therapies are altered by clinical characteristics, previous analyses have suggested sex and BMI are associated with glycemic response to both therapies. In ADOPT, risk of therapy failure were lower for obese and female subgroups with thiazolidinediones compared to sulfonylureas, but an interaction was not tested for and the difference in glycemic trajectory was not examined.(7) Increased response for obese female patients with thiazolidinediones and for male patients with sulfonylureas has been found in observational studies.(12, 13) but the impact of this in terms of stratification has not been assessed. We have previously shown that markers of insulin resistance including BMI are associated with reduced glycemic response to DPP4 inhibitors but not glucagon-like peptide 1 (GLP-1) receptor agonists,(33, 34) but evidence for other agents is limited.(35, 36)

Previous studies have also found sex and BMI alter the risk of side effects. The increase in fracture risk with thiazolidinediones applies mainly to post-menopausal women and is consistent within trials.(10, 11, 14, 37) We found hypoglycemia risk with sulfonylureas was similar across subgroups even though

glycemic response differed, and this needs further investigation. Whilst our study shows absolute risk of oedema with thiazolidinediones was highest in the obese female subgroup that had the greatest response, further study is required to fully evaluate the association between glycemic response and the risk of common side effects for these therapies.

Limitations

Our study has limitations. The results do not allow prediction at an individual level, however we present subgroup estimates that will better reflect the likely outcome for an individual patient within that subgroup than outcome estimates derived from whole trial populations. Rosiglitazone, the thiazolidinedione used in both trials analysed in our study, has been withdrawn in many countries due to concerns over cardiovascular safety.(38) Routine clinical data support a thiazolidinedione class effect of differential response by sex and obesity but trial data were not made available to repeat our analysis for pioglitazone. Previous meta-analyses suggest that the risks of oedema and fracture are similar with both drugs, further supporting the generalizability of our findings to pioglitazone.(37, 39) For sulfonylureas, a similar pattern of results was observed in ADOPT (glibenclamide), RECORD (52% glimepiride, 30% gliclazide, 18% glibenclamide), and routine clinical data (including a gliclazide only analysis), supporting a sulfonylurea class effect. In CPRD, for the one year glycemic response analysis we excluded non-adherent patients and those whose anti-hyperglycemic therapy was altered (potentially due to poor response, very good response, or poor tolerance) within the first year, and this could have accounted for the differences we observed when comparing sulfonylurea and thiazolidinedione therapy. However, we saw a similar pattern of glycemic response differences using time to failure and mixed effect models

which both included all individuals with at least one on-therapy HbA_{1c} measure for up to five years. The CPRD time to failure analysis was also limited as individuals whose treatment was intensified below the HbA_{1c} failure threshold of 8.5% were censored rather than defined as experiencing therapy failure. A strength of the CPRD analysis is the demonstration of consistent results with all three analytical approaches, each with their own strengths and weaknesses. Measured or unmeasured baseline differences between individuals could have explained findings in the routine data, but are very unlikely to explain the differences we observed in the randomized clinical trials, further highlighting the strength of our study design. Over 90% of people in the datasets studied were White Caucasian, limiting the applicability of our findings to other racial groups, a common problem with trials in type 2 diabetes. Additional data would be required to answer whether there are differences in people of South Asian, Hispanic or Black origin, where fat distribution can be markedly different and a different obesity cut-off may be appropriate.(40) A particular benefit in cardiovascular outcome for non-white ethnicities has recently been demonstrated for SGLT2 inhibitors,(41, 42) emphasising the importance of considering ethnicity when undertaking stratified medicine research. We found both older age at diagnosis and lower eGFR were associated with greater response to both therapies. This may relate to increased medication adherence in older individuals (renal function declines with age), but further study is required to interrogate this and to establish if associations with the same directions of effect are observed for other type 2 diabetes therapies.

The ideal stratified approach would be based on cardiovascular endpoints rather than the intermediary measure of glycemic response. In this analysis we were underpowered to detect differences for cardiovascular outcomes in

RECORD (the primary trial analysis showed no difference between rosiglitazone and sulfonylureas or metformin), or rarer side effects such as heart failure.(14) Given recent trials demonstrating cardiovascular benefits with SGLT2 inhibitors and GLP-1 receptors agonists each required over 7000 high-risk participants,(42, 43) it may be that impractically large trials are required for stratification of cardiovascular endpoints.

Future research

Evaluation of the risks and benefits of newer therapies such as DPP4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists will require routine clinical data from large numbers of people alongside shared head-to-head drug trial data, and will be possible in the near future. Given the greater expense of newer therapies cost-effectiveness evaluation will be necessary in this work. The ongoing GRADE study will give important long-term head-to-head comparative effectiveness data on second-line treatment with insulin, DPP4 inhibitor, GLP-1 receptor agonist and sulfonylurea therapy.(44)

Further mechanistic studies are required to interrogate the mechanisms underlying differential response to sulfonylureas and thiazolidinediones. Thiazolidinediones act through the adipocyte and so it is likely any increase in the number of adipocytes will improve glycemic response. This provides a potential explanation for our findings as women, compared to men, have more adipocytes as they have a higher whole body percentage fat mass and obese subjects have more adipocytes than non-obese subjects.(45) The reduced insulin sensitivity seen in obesity is likely to explain the reduced response to

sulfonylureas that predominantly stimulate insulin secretion by the beta-cell. The consistently better response seen in males to sulfonylureas was unexpected and further studies are required to define the mechanism of this observation.

Clinical Implications

The sex and obesity subgroup-specific estimates presented in this study will allow a much more informed discussion between clinicians and patients of the benefits and risks of sulfonylureas and thiazolidinediones, at no cost. We recommend this discussion with an individual is based around the appropriate sex and obesity subgroup-specific estimates presented for the two therapies in the Subgroup data summary (Supplementary material). Whether this alters a decision on therapy will depend on the individual circumstances of the patient, as the trade-off between early-response, long-term durability and risk of side-effects will be different. In current guidelines sulfonylureas and thiazolidinediones are the two therapies recommended after metformin in settings where cost is the major issue,(46) and so our results may be especially applicable for the 80% of people with type 2 diabetes who live in low or middle income countries.

Conclusion

Simple clinical characteristics alter the benefits and risks of type 2 diabetes therapy with sulfonylureas and thiazolidinediones. Our novel and practical framework for stratification research can be applied in type 2 diabetes and other chronic conditions, and has great potential to improve output from future studies using shared trial data.

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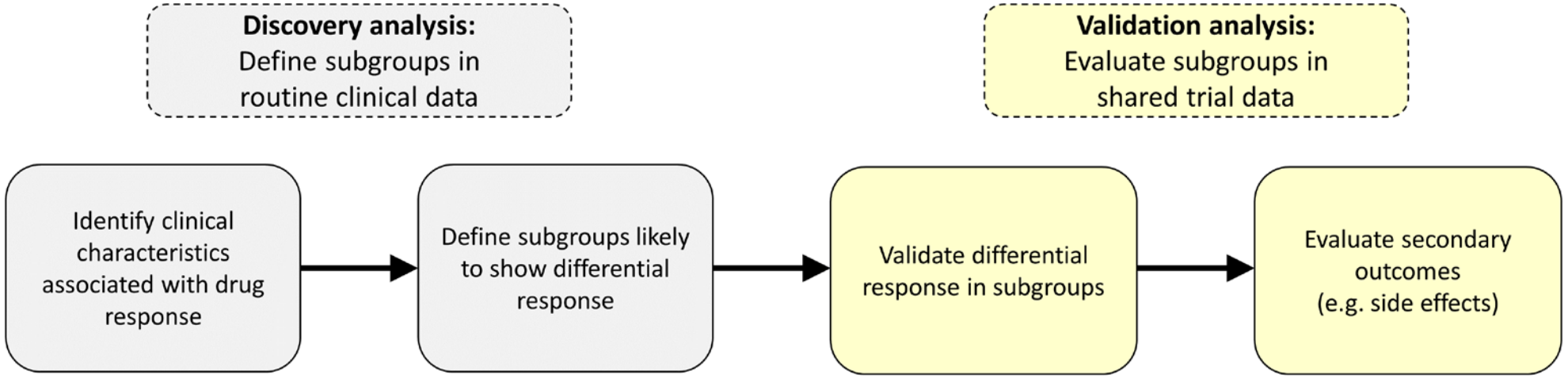
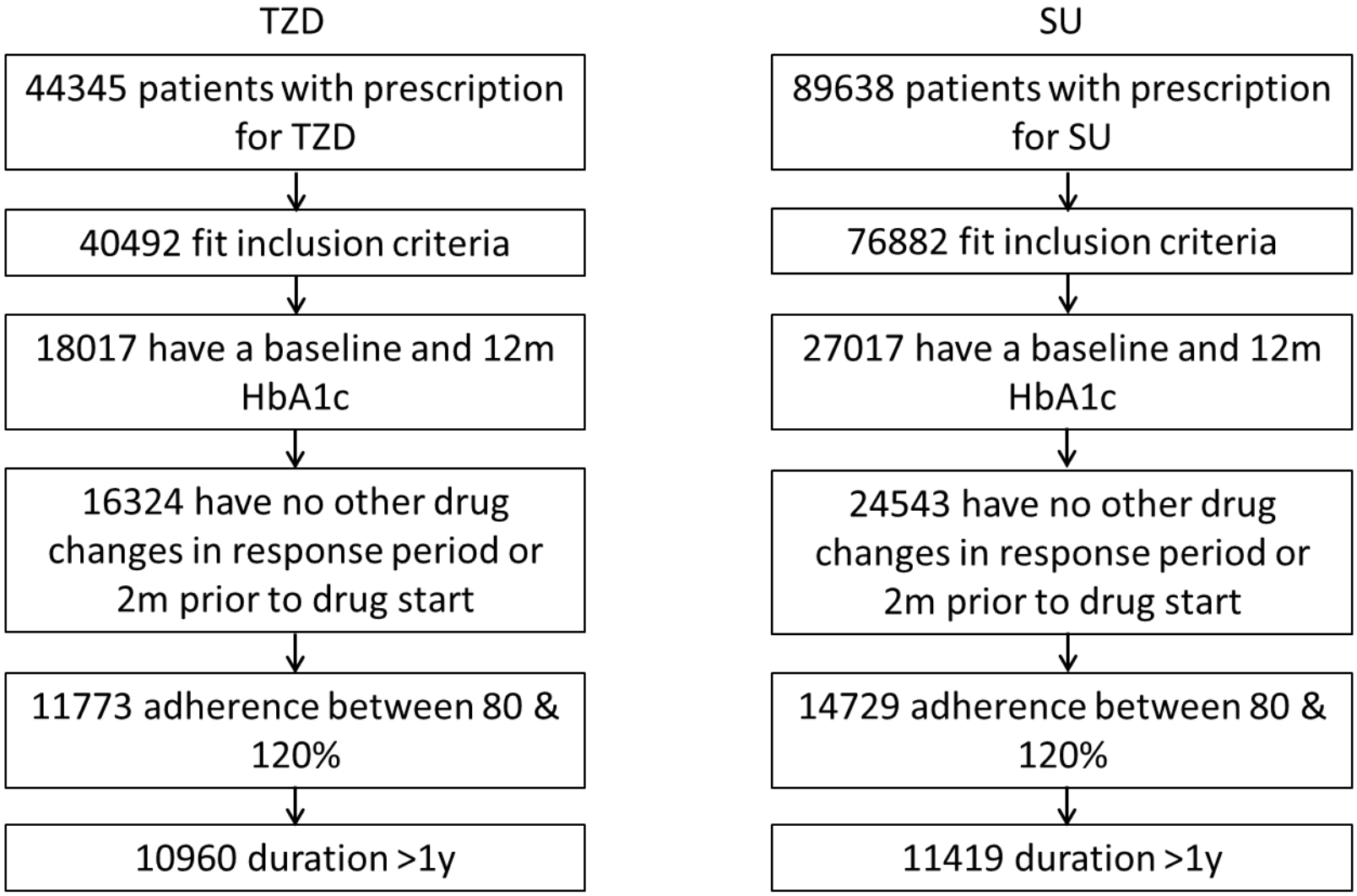
Supplementary Material

Supplementary Figure 1: A framework for stratification research using routine clinical and shared trial data



Supplementary Figure 2: Flow diagram showing the determination of the final CPRD datasets used in analysis, based on patients treated with thiazolidinediones (TZD) or sulfonylureas (SU). Adherence measured by the medicine possession ratio.

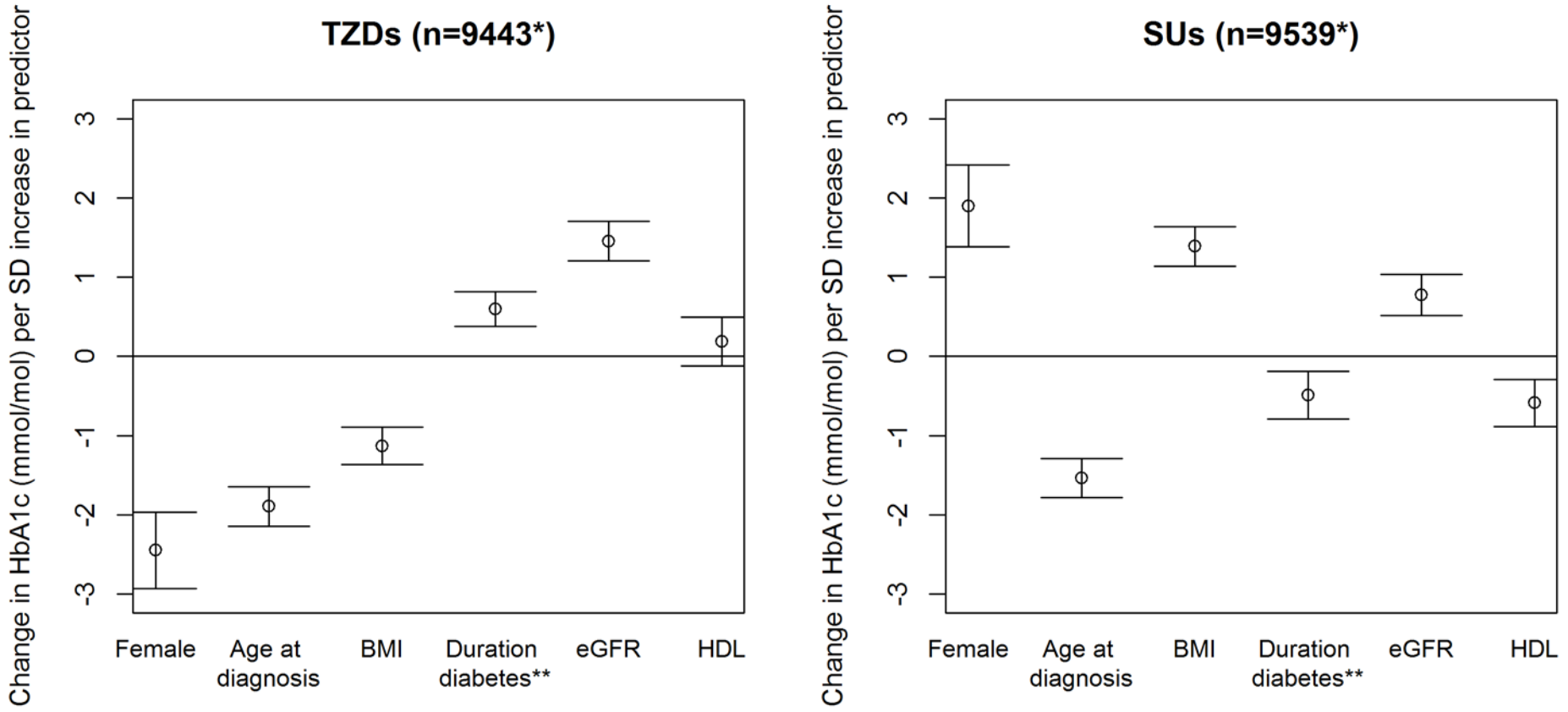


Supplementary Table 1: CPRD population baseline characteristics split by cohorts treated with thiazolidinediones (TZD) and sulfonylureas (SU). Data presented for the whole group and 4 subgroups defined by obesity (BMI>30kg/m^2) and sex.

	All		Non Obese Male		Non Obese Female		Obese Male		Obese Female	
TZDs	**n**	**Mean(SD)**	**n**	**Mean(SD)**	**n**	**Mean(SD)**	**n**	**Mean(SD)**	**n**	**Mean(SD)**
Age diag (y)	10960	57.0 (9.9)	2825	57.6 (9.7)	1521	61.1 (9.9)	3030	54.7 (9.3)	2064	56.1 (9.7)
Age (y)	10960	63.7 (10.4)	2825	65.3 (10.0)	1521	68.6 (10.1)	3030	60.6 (9.6)	2064	62.0 (10.0)
Duration Diabetes* (y)	10960	5.4 (2.6, 10.9)	2825	6.2 (3.0, 12.8)	1521	6.0 (2.9, 12.4)	3030	4.8 (2.4, 9.4)	2064	4.7 (2.4, 9.4)
BMI* (kg/m^2)	9443	30.9 (25.8, 37.0)	2825	26.7 (24.4, 29.2)	1521	26.2 (23.6, 29.1)	3030	34.6 (30.9, 38.8)	2064	35.9 (31.3, 41.3)
Male (%)	10960	62%	2825	100%	0	0%	3030	100%	0	0%
Dose (weighted mean % max)**	10703	50 (50, 66.7)	2761	50 (50, 66.7)	1488	50 (49.8, 66.7)	2963	50 (50, 66.7)	2011	50 (50, 66.7)
Adherence (%)	10960	101.1 (8.0)	2825	101.0 (8.0)	1521	101.4 (7.9)	3030	100.9 (8.1)	2064	101.2 (7.9)
HbA1c (mmol/mol)	10960	71.0 (14.2)	2825	69.4 (13.0)	1521	70.7 (14.8)	3030	71.8 (14.4)	2064	71.6 (15.0)
	All		**Non Obese Male**		**Non Obese Female**		**Obese Male**		**Obese Female**	
SUs	**n**	**Mean(SD)**	**n**	**Mean(SD)**	**n**	**Mean(SD)**	**n**	**Mean(SD)**	**n**	**Mean(SD)**
Age diag (y)	11419	59.3 (10.8)	2976	60.2 (10.4)	1603	64.5 (10.9)	2856	55.6 (9.6)	2103	57.8 (10.2)
Age (y)	11419	64.6 (10.8)	2976	65.8 (10.3)	1603	69.7 (10.8)	2856	60.7 (9.9)	2103	62.9 (10.3)
Duration Diabetes* (y)	11419	4.2 (2.1, 8.5)	2976	4.4 (2.1, 9.1)	1603	4.2 (2.1, 8.4)	2856	4.2 (2.2, 8.1)	2103	4.2 (2.1, 8.2)
BMI* (kg/m^2)	9539	30.6 (25.4, 36.8)	2976	26.5 (24.1, 29.1)	1603	26.0 (23.3, 29.1)	2856	34.6 (30.9, 38.8)	2103	36.0 (31.4, 41.2)
Male (%)	11419	61%	2976	100%	0	0%	2856	100%	0	0%
Dose (weighted mean % max)**	10958	25 (25, 44.5)	2853	25 (25, 37.8)	1541	25 (23.9, 33.2)	2745	25 (25, 50)	2011	25 (25, 47.7)
Adherence (%)	11419	101.0 (8.6)	2976	100.7 (8.4)	1603	101.4 (8.5)	2856	100.8 (8.7)	2103	101.4 (8.7)
HbA1c (mmol/mol)	11419	70.7 (16.0)	2976	69.4 (15.7)	1603	68.4 (15.0)	2856	71.9 (15.5)	2103	71.3 (16.1)

*skewed data so presented as geometric mean (SD range). **Dose presented as median (IQR)

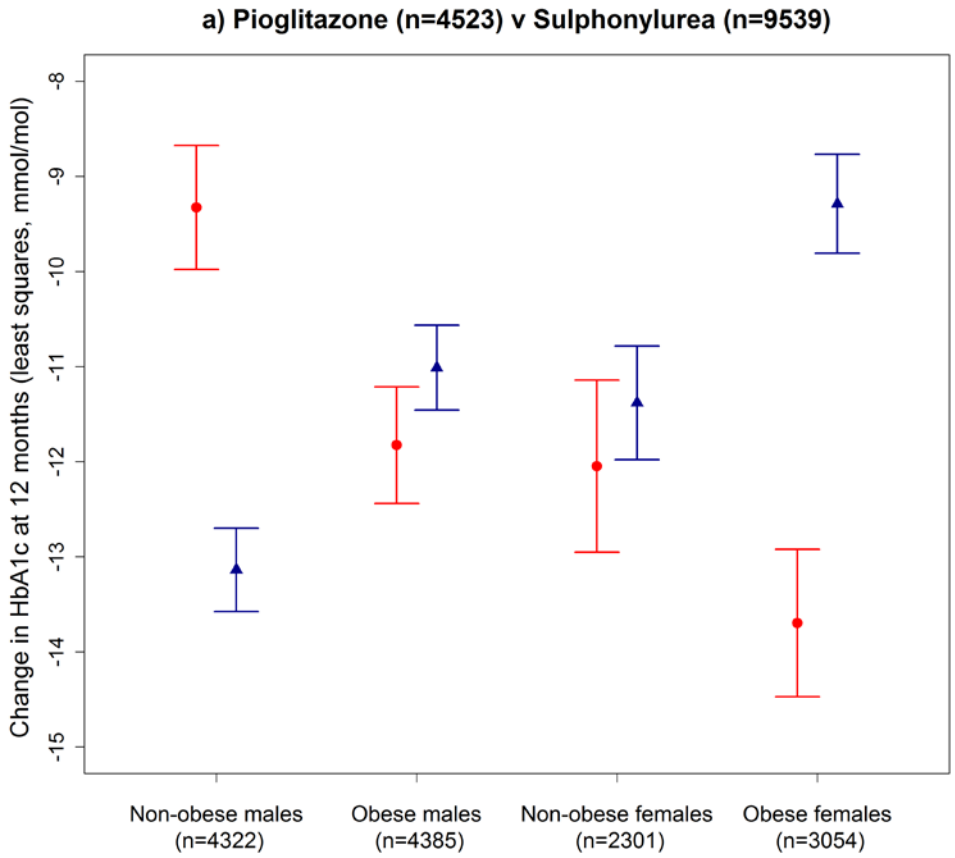
Supplementary Figure 3: Coefficients for predictors of one year response with thiazolidinediones (TZDs) or sulfonylureas (SUs) in CPRD. Data presented as beta coefficient from regression analysis (change in HbA1c per one unit increase in each predictor) with 95% confidence intervals as error bars. All predictors, except for baseline HbA1c, are adjusted for baseline HbA1c.

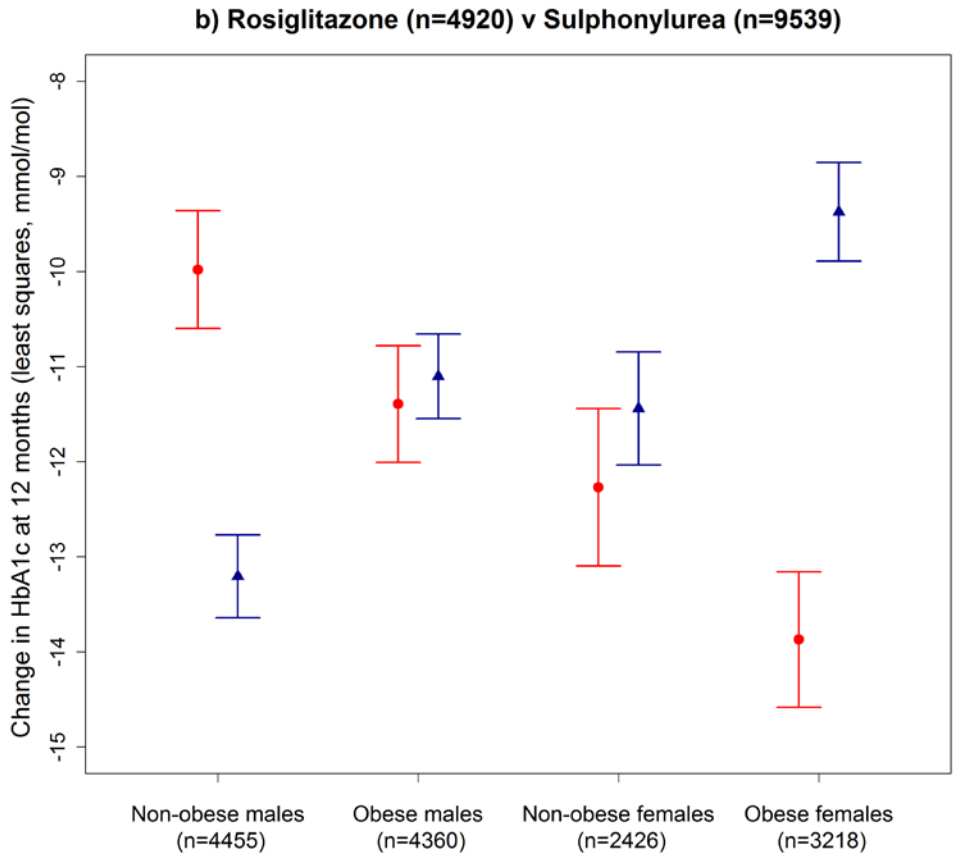


* TZD n=8291, SU n=8055 with valid baseline eGFR measure. TZD n=6184, SU n=5623 with valid baseline HDL measure.

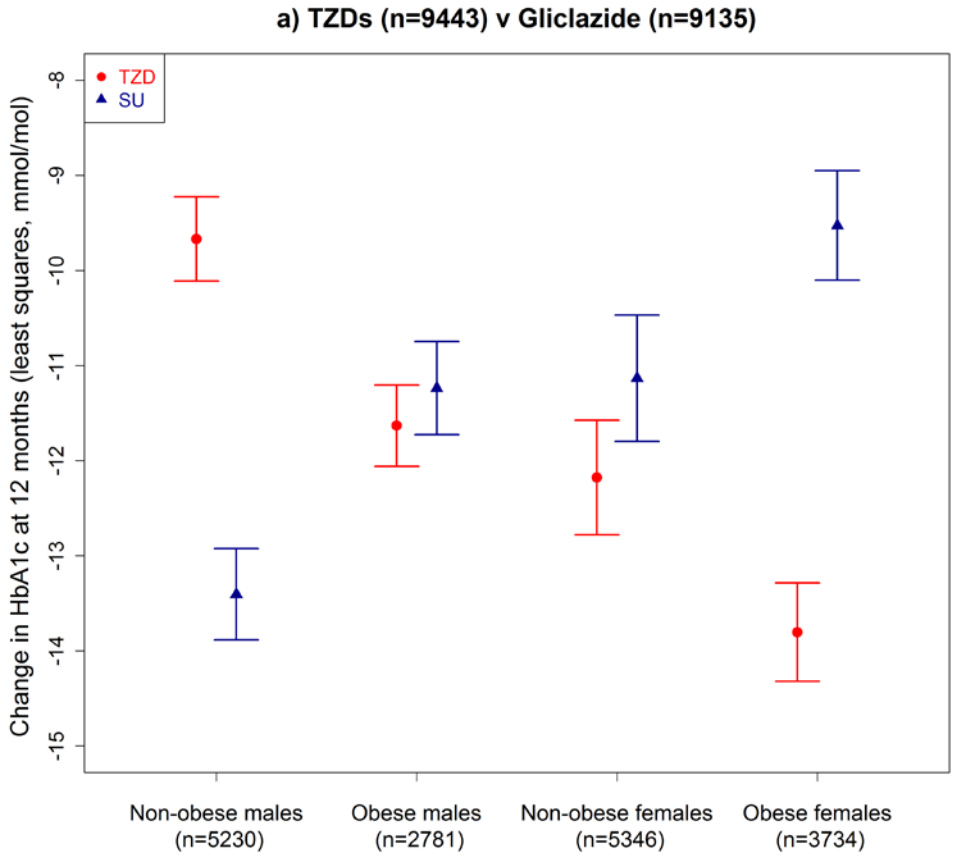
** Duration results presented but association was non-linear and showed poor model fit

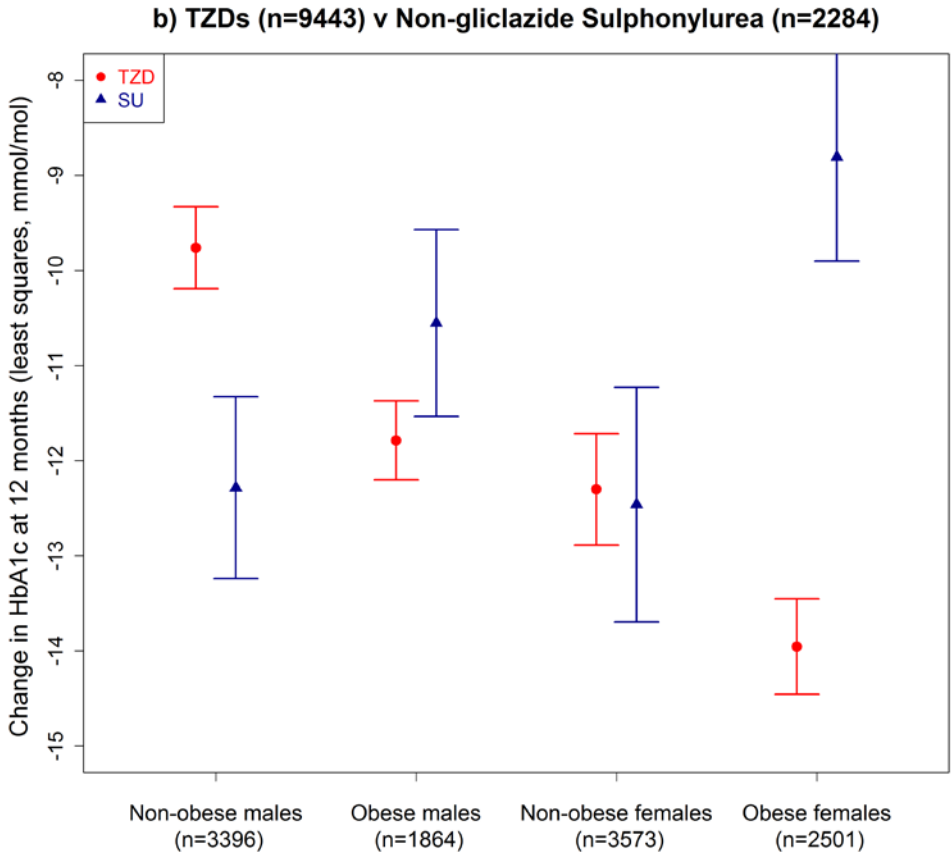
Supplementary Figure 4a: CPRD one year response with a) Pioglitazone and b) Rosiglitazone (red dots), compared to sulfonylurea (blue triangles), by sex and obesity defined subgroups. Data are presented as baseline adjusted mean change in HbA1c ± 95% CI





Supplementary Figure 4b: CPRD one year response with a) Gliclazide and b) Non-gliclazide sulfonylureas (blue triangles), compared to thiazolidinediones (red dots), by sex and obesity defined subgroups. Data are presented as baseline adjusted mean change in HbA1c ± 95% CI





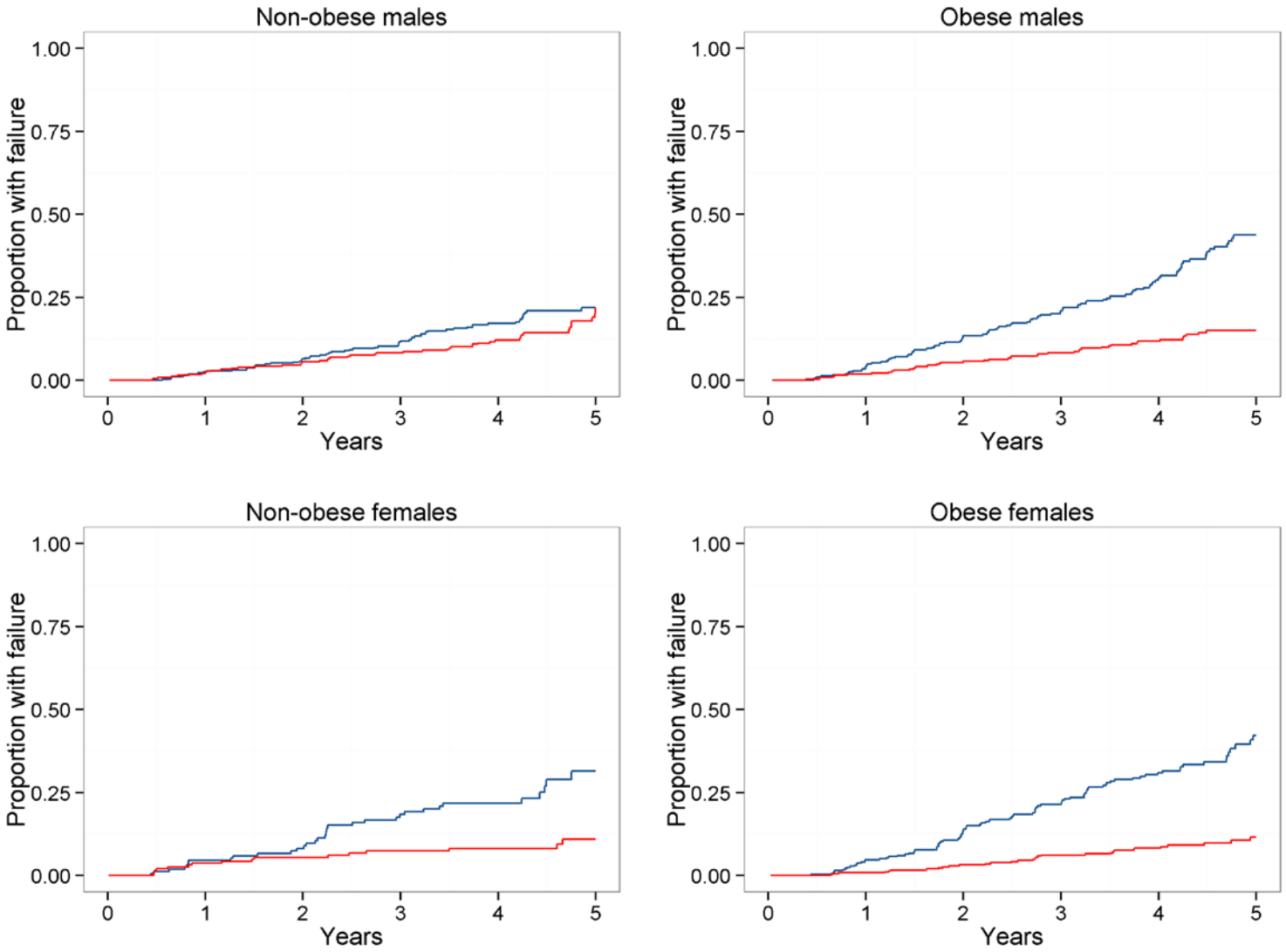
Supplementary Table 2: Baseline characteristics for patients in the ADOPT trial, by sex and obesity defined subgroup and therapy. Data presented as mean (SD) or *median (IQR)

	Non-obese Male		Obese Male		Non-obese Female		Obese Female	
	TZD	**SU**	**TZD**	**SU**	**TZD**	**SU**	**TZD**	**SU**
Patients (n)	373	395	402	387	208	174	407	379
Age (years)	57.8 (10.0)	57.9 (9.9)	55.2 (9.5)	55.4 (9.3)	58.2 (10.1)	59.7 (10.4)	55.0 (9.9)	54.7 (10.6)
Ethnic origin (white)	330 (88%)	362 (92%)	358 (89%)	347 (90%)	173 (83%)	161 (93%)	356 (87%)	326 (86%)
Time since diagnosis	0.80 (0.89)	0.89 (0.91)	0.80 (0.88)	0.84 (0.89)	0.85 (0.85)	0.86 (1.23)	0.79 (0.83)	0.77 (0.82)
Weight (kg)	81.9 (9.3)	82.6 (9.8)	106.7 (17.7)	108.1 (17.8)	68.7 (8.4)	69.2 (7.9)	97.2 (17.2)	97.1 (18.4)
BMI	26.9 (2.1)	27.0 (2.0)	34.9 (4.7)	35.2 (4.6)	26.6 (2.5)	26.5 (2.5)	37.2 (6.0)	37.2 (5.9)
Waist to hip ratio	0.97 (0.06)	0.96 (0.08)	1.00 (0.08)	1.00 (0.06)	0.89 (0.09)	0.89 (0.09)	0.90 (0.08)	0.90 (0.08)
HbA1c (mmol/mol)	56.7 (11.0)	56.2 (11.2)	57.1 (10.1)	57.3 (9.5)	57.6 (10.3)	56.7 (10.3)	56.8 (9.1)	57.2 (9.3)
Fasting glucose (mmol/l)	8.4 (1.6)	8.4 (1.4)	8.5 (1.5)	8.6 (1.6)	8.4 (1.3)	8.5 (1.8)	8.4 (1.3)	8.4 (1.4)
Insulin sensitivity HOMA-S (%)*	46 (31-64)	45 (32-63)	28 (20-39)	28 (20-39)	43 (32-59)	41 (29-56)	27 (19-39)	26 (20-36)
Beta-cell function HOMA-B (%)*	59 (46-79)	59 (47-73)	75 (59-95)	74 (57-94)	58 (46-73)	64 (46-81)	74 (58-91)	76 (59-94)
Triglycerides (mmol/l)*	1.7 (1.2-2.4)	1.6 (1.1-2.4)	2.0 (1.4-3.0)	1.9 (1.4-2.7)	1.7 (1.2-2.3)	1.6 (1.2-2.3)	1.9 (1.4-2.6)	1.8 (1.4-2.4)
LDL cholesterol (mmol/l)*	3.1 (2.5-3.7)	3.0 (2.5-3.6)	3.1 (2.5-3.6)	3.1 (2.5-3.7)	3.3 (2.6-3.9)	3.4 (2.7-4.0)	3.2 (2.7-3.8)	3.1 (2.6-3.8)
HDL cholesterol (mmol/l)*	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.1 (0.9-1.3)	1.1 (0.9-1.3)	1.4 (1.2-1.6)	1.4 (1.2-1.6)	1.3 (1.1-1.5)	1.3 (1.1-1.5)

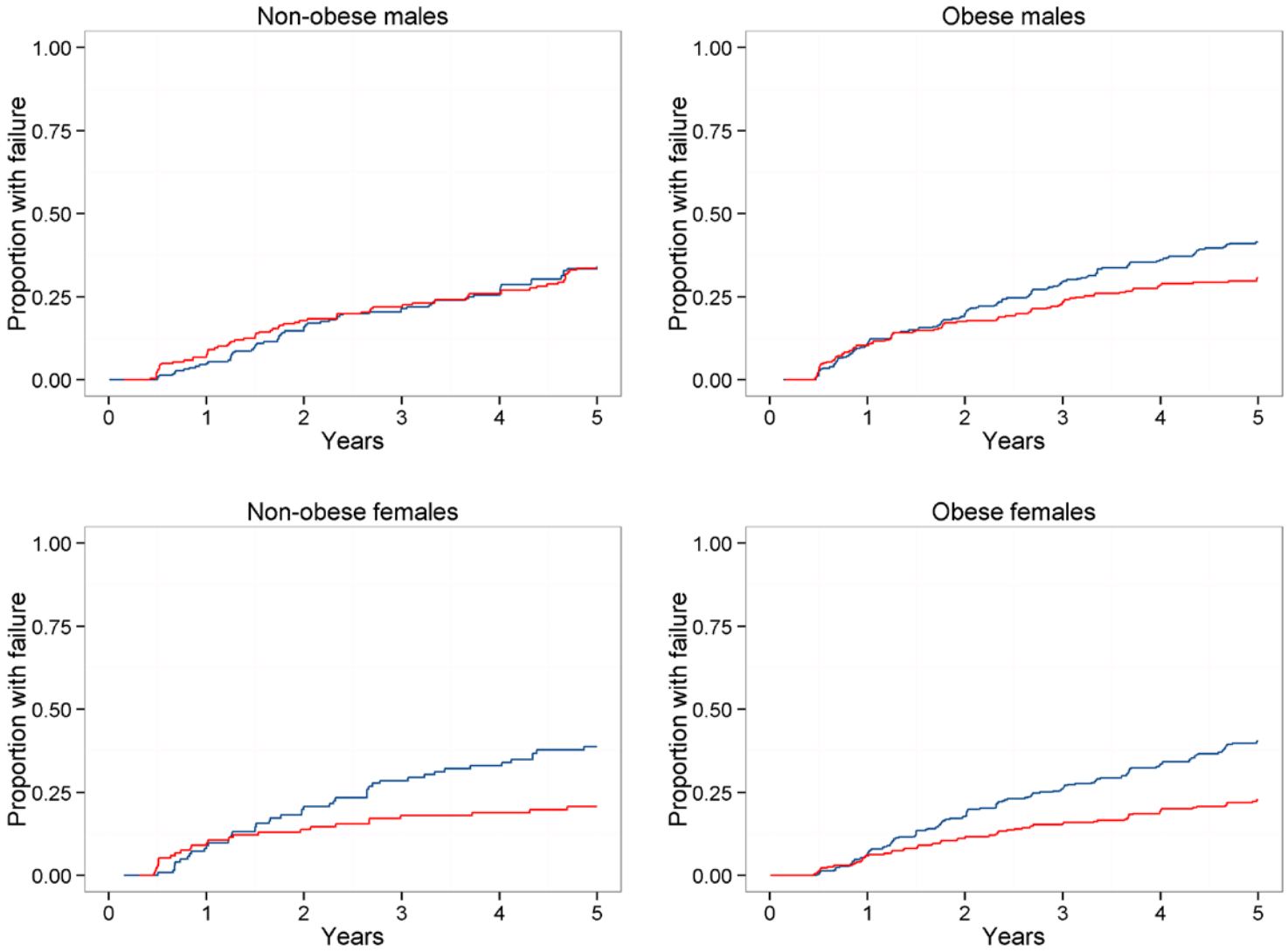
Supplementary Table 3: Baseline characteristics for patients in the RECORD trial, by sex and obesity defined subgroup and therapy. Data presented as mean (SD) or *median (IQR)

	Non-obese Male		Obese Male		Non-obese Female		Obese Female	
	TZD	**SU**	**TZD**	**SU**	**TZD**	**SU**	**TZD**	**SU**
Patients (n)	240	228	361	356	137	127	379	394
Age (years)	58.2 (8.4)	57.9 (8.5)	55.5 (7.8)	55.7 (8.0)	59.1 (7.7)	59.2 (8.2)	56.9 (7.8)	57.5 (7.8)
Ethnic origin (white)	237 (99%)	223 (98%)	359 (99%)	351 (99%)	135 (99%)	122 (96%)	374 (99%)	391 (99%)
Time since diagnosis	6.4 (4.4)	6.9 (4.4)	5.7 (3.7)	6.0 (4.4)	6.9 (4.9)	7.1 (4.7)	6.1 (4.2)	6.1 (4.3)
Weight (kg)	85.7 (8.2)	86.2 (8.2)	106.6 (14.8)	106.0 (14.4)	72.9 (7.2)	73.1 (7.3)	93.4 (13.1)	92.4 (14.1)
BMI	27.8 (1.5)	27.8 (1.5)	34.7 (3.9)	34.3 (4)	27.7 (1.5)	27.6 (1.7)	36.0 (4.4)	35.8 (4.9)
Waist to hip ratio	0.97 (0.05)	0.98 (0.06)	1.01 (0.06)	1.01 (0.06)	0.90 (0.07)	0.91 (0.07)	0.92 (0.07)	0.92 (0.07)
HbA1c (mmol/mol)	61.4 (7.3)	61.2 (7.2)	62.1 (7.5)	62.9 (7.7)	61.5 (7.3)	62.0 (6.8)	62.4 (7.3)	62.0 (6.7)
Fasting glucose (mmol/l)	9.5 (2.0)	9.4 (2.0)	9.6 (2.3)	9.9 (2.2)	9.1 (2.0)	9.1 (1.9)	9.4 (1.9)	9.5 (2.2)
Insulin sensitivity HOMA-S (%)*	87 (60-131)	93 (60-123)	52 (38-74)	52 (34-77)	80 (55-127)	79 (57-130)	58 (41-79)	58 (39-83)
Beta-cell function HOMA-B (%)*	29 (21-39)	30 (20-42)	42 (30-60)	42 (25-58)	33 (23-42)	32 (22-47)	40 (30-54)	41 (28-57)
Triglycerides (mmol/l)*	1.8 (1.3-2.5)	1.8 (1.2-2.7)	2.2 (1.7-3.0)	2.1 (1.4-3.1)	1.8 (1.3-2.7)	1.8 (1.3-2.3)	2.1 (1.6-2.7)	2.0 (1.5-2.8)
LDL cholesterol (mmol/l)*	3.2 (2.6-3.6)	3.2 (2.6-3.7)	3.0 (2.5-3.6)	3.0 (2.4-3.6)	3.3 (2.8-3.9)	3.3 (2.8-3.9)	3.3 (2.7-3.9)	3.3 (2.6-3.9)
HDL cholesterol (mmol/l)*	1.1 (1.0-1.3)	1.2 (1-1.3)	1.1 (0.9-1.2)	1.1 (0.9-1.2)	1.3 (1.1-1.5)	1.3 (1.1-1.5)	1.2 (1.1-1.4)	1.2 (1.1-1.4)

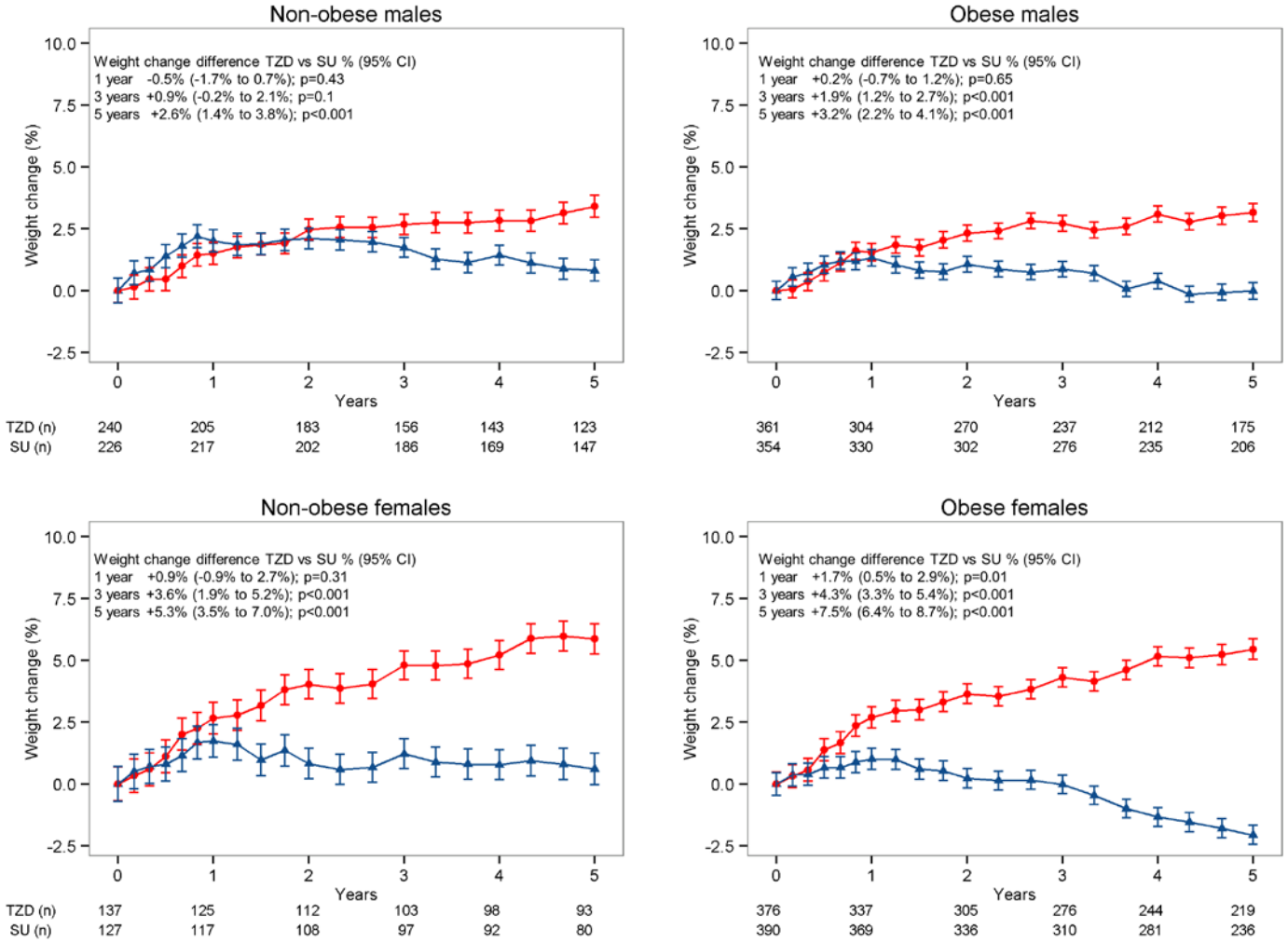
Supplementary Figure 5: ADOPT Kaplan–Meier estimates of the cumulative incidence of monotherapy failure with thiazolidinediones (red) and sulfonylureas (blue) over 5 years by sex and obesity defined subgroup. Failure defined as confirmed fasting plasma glucose ≥ 180 mg/dl.



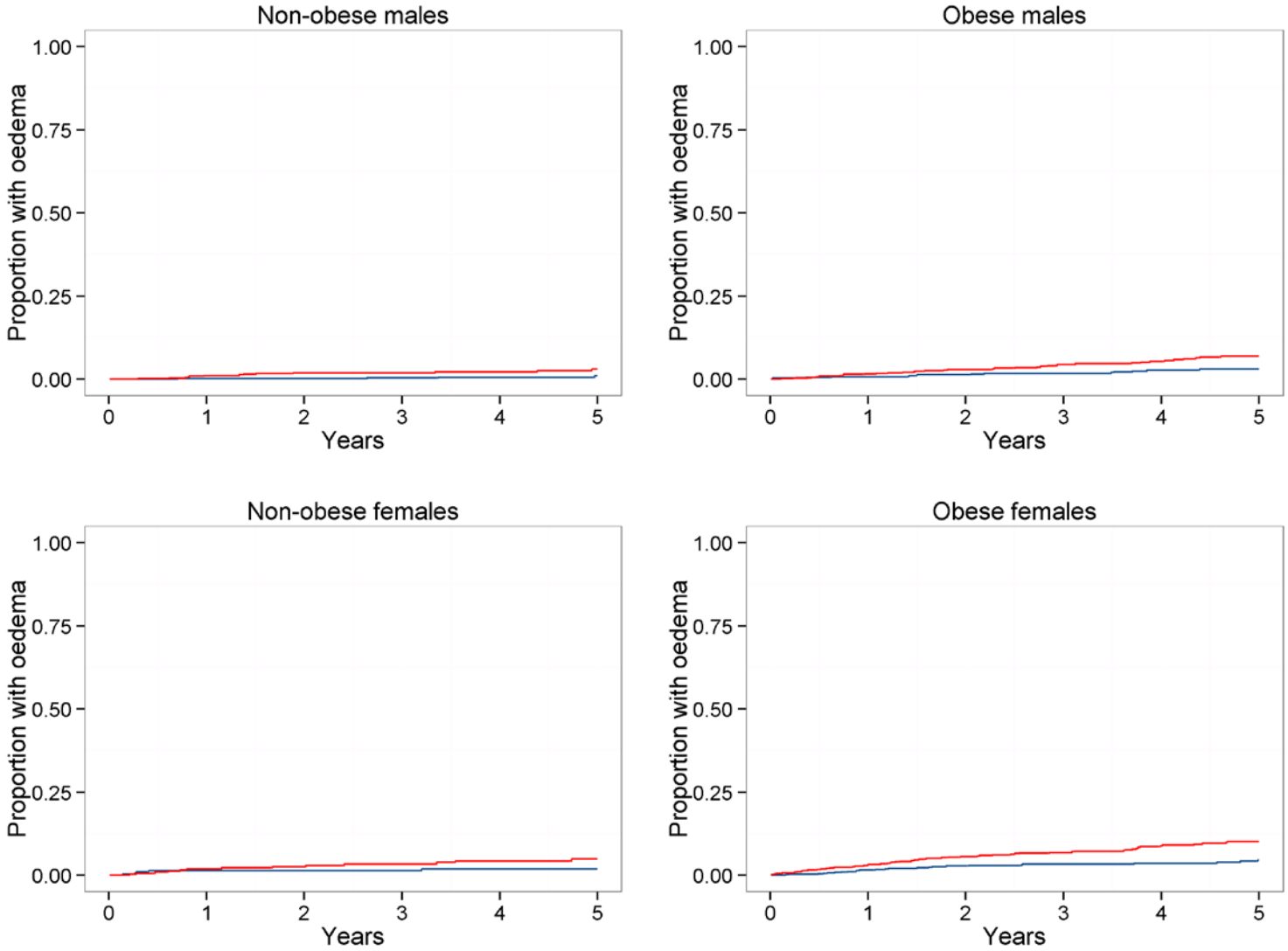
Supplementary Figure 6: RECORD Kaplan–Meier estimates of the cumulative incidence of dual therapy failure with thiazolidinediones (red) and sulfonylureas (blue) over 5 years by sex and obesity defined subgroup. Failure defined as confirmed HbA1c ≥8.5%



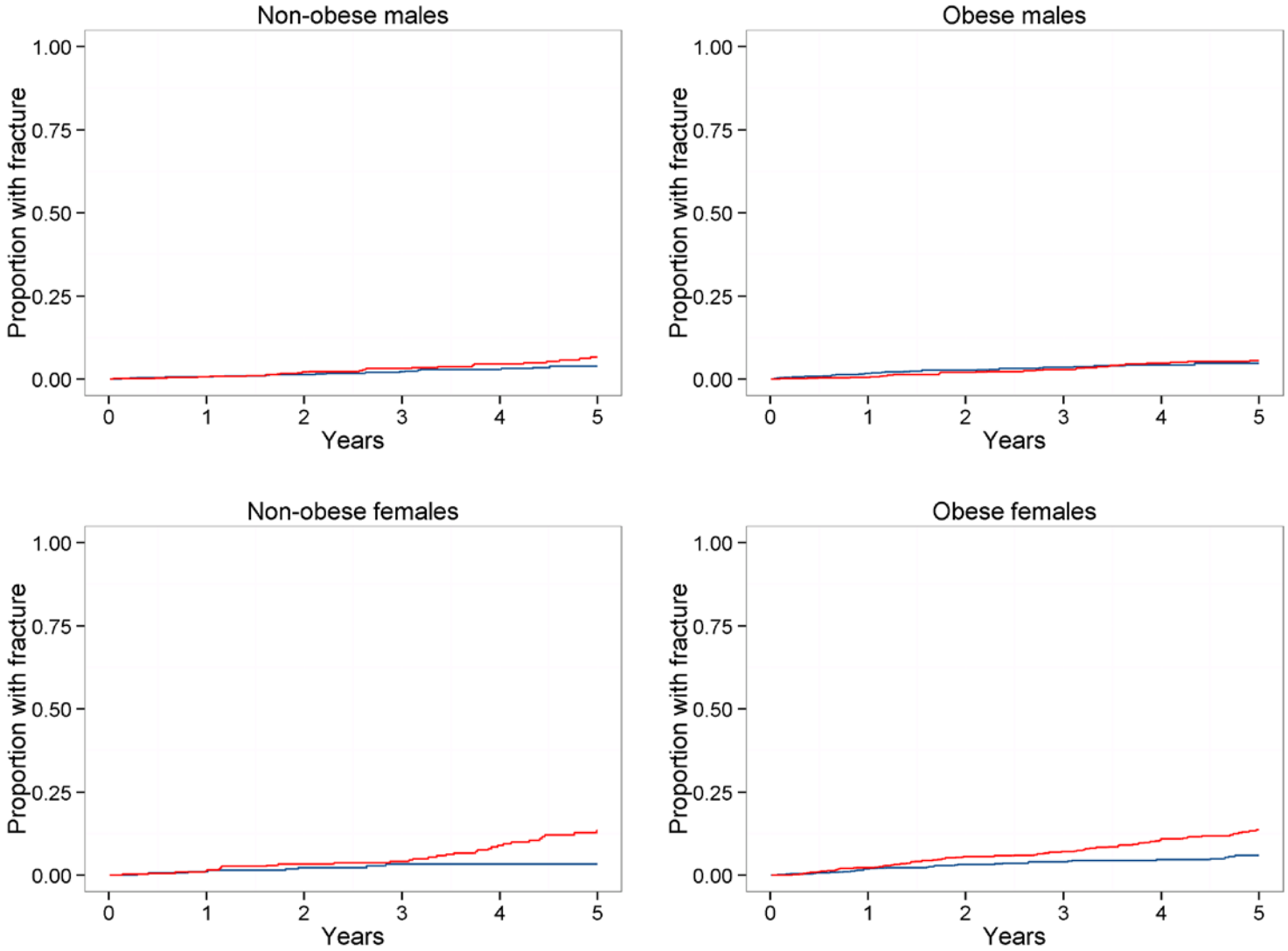
Supplementary Figure 7: RECORD percentage weight change from baseline over 5 years with thiazolidinediones (red dots) and sulfonylureas (blue triangles), by sex and obesity defined subgroup. Data are presented as means at each study visit ± standard error from mixed effects models, adjusted for baseline weight. Number (n) per year presented below plots for each therapy and subgroup.



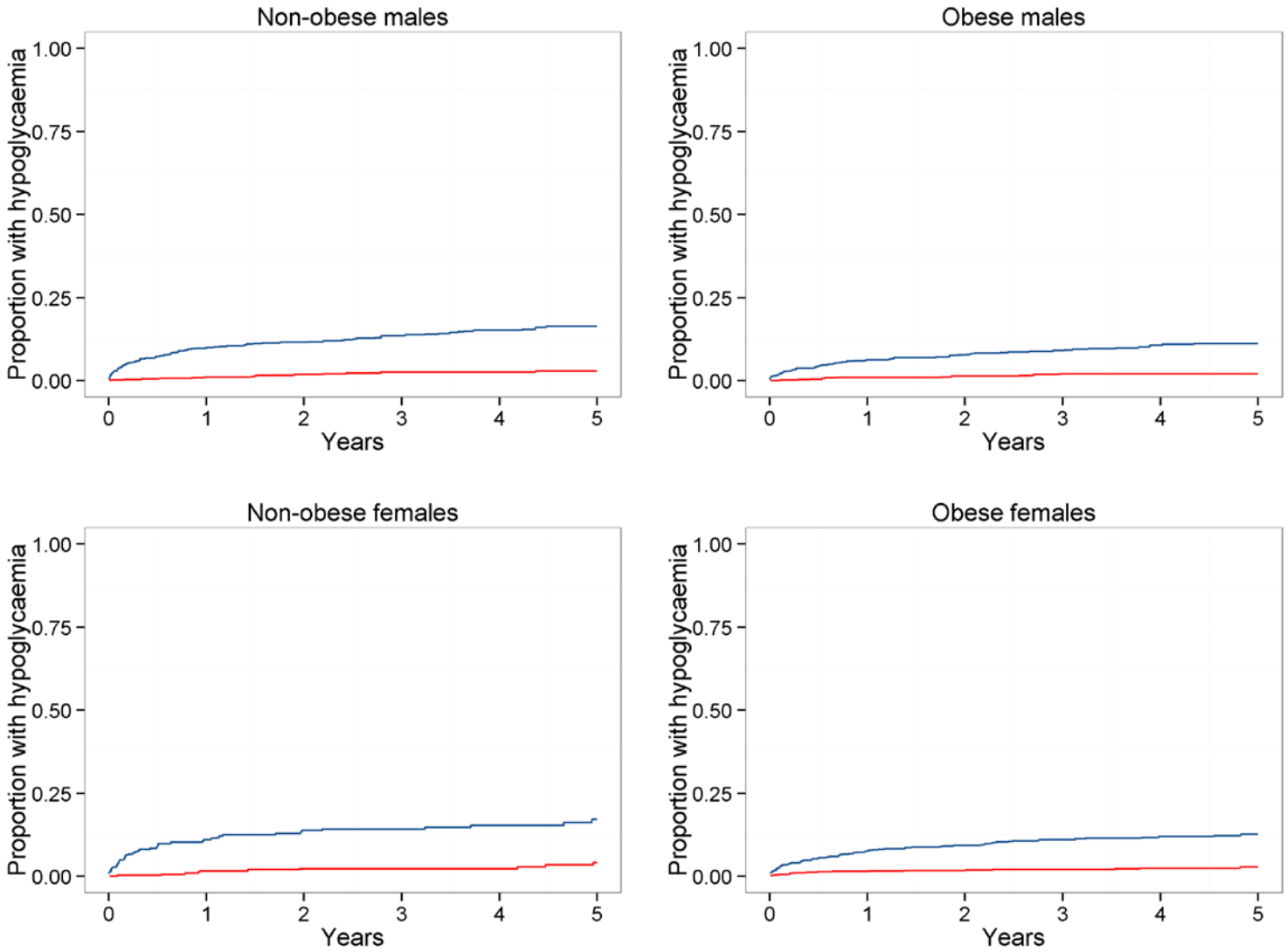
Supplementary Figure 8: ADOPT & RECORD combined Kaplan–Meier estimates of the cumulative incidence of moderate/severe oedema over 5 years with thiazolidinediones (red) and sulfonylureas (blue)



Supplementary Figure 9: ADOPT & RECORD combined Kaplan–Meier estimates of the cumulative incidence of fracture (any) over 5 years with thiazolidinediones (red) and sulfonylureas (blue).



Supplementary Figure 10: ADOPT & RECORD combined Kaplan–Meier estimates of the cumulative incidence of moderate/severe hypoglycaemia over 5 years with thiazolidinediones (red) and sulfonylureas (blue)



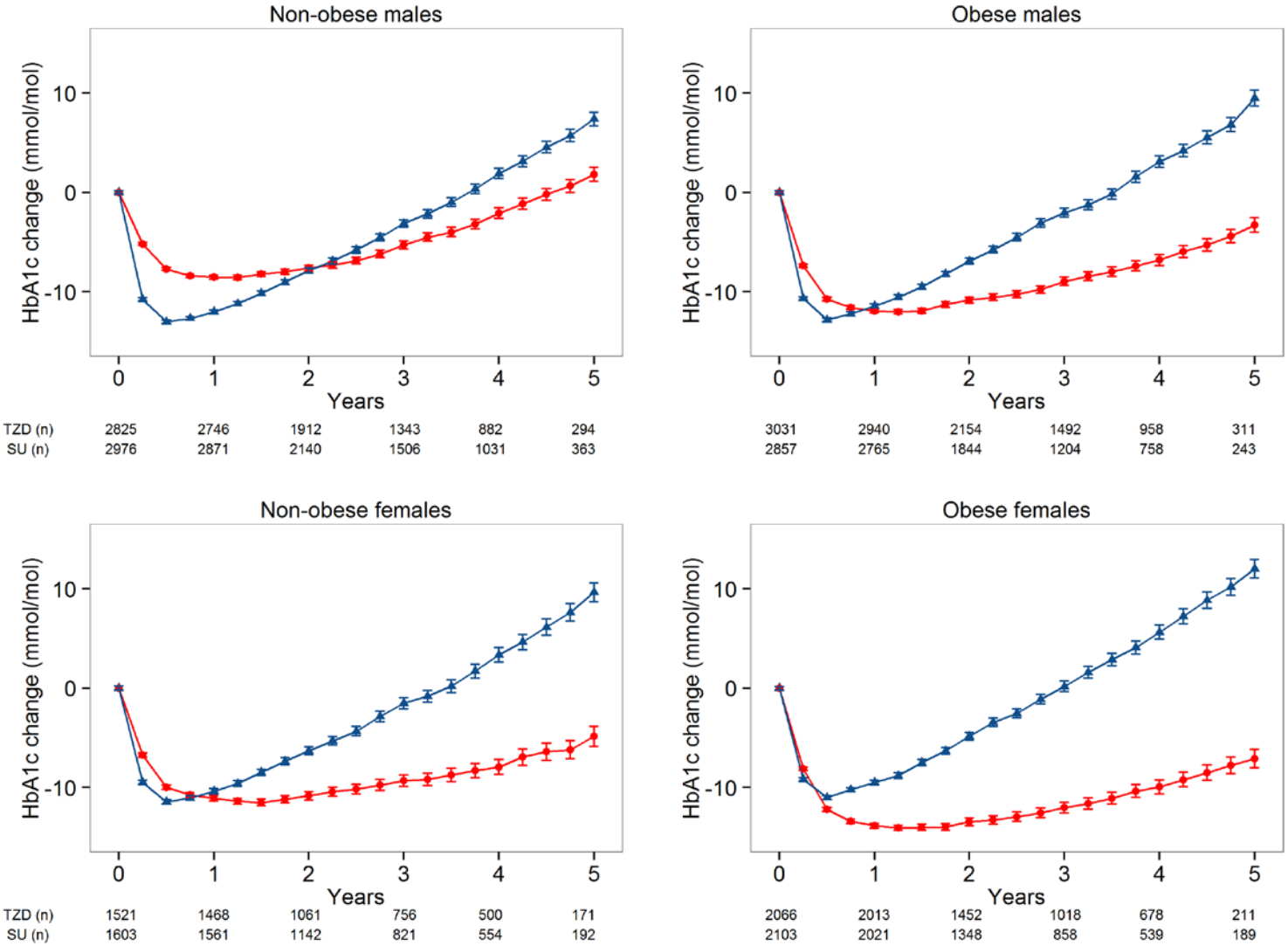
Supplementary Table 4: ADOPT absolute and relative risk of side effects over 5 years with thiazolidinediones (TZD) and sulfonylureas (SU), by sex and obesity defined subgroup. Relative risks presented as hazard ratios (95% CI) for TZD compared to SU.

Side effect	No. of patients		No. of events		Absolute 5 year risk (%)		Hazard ratio*	p value
	TZD	SU	TZD	SU	TZD	SU		
Non-obese males								
Oedema	367	392	16	12	6%	5%	1.44 (0.68-3.03)	0.34
Oedema (Moderate/Severe)	367	392	6	3	2%	2%	2.16 (0.54-8.63)	0.28
Fracture	373	395	12	12	4%	5%	1.06 (0.48-2.37)	0.88
Hypoglycaemia (All)	373	395	33	161	10%	49%	0.18 (0.12-0.25)	<0.01
Hypoglycaemia (Moderate/Severe)	373	395	12	74	4%	22%	0.16 (0.09-0.29)	<0.01
Hypoglycaemia (Severe)	24 events total across all 4 subgroups with both therapies - 21 SU, 3 TZD							
Obese males								
Oedema	379	363	52	34	19%	13%	1.33 (0.86-2.05)	0.20
Oedema (Moderate/Severe)	379	363	13	10	5%	4%	1.10 (0.48-2.51)	0.83
Fracture	402	387	18	14	6%	5%	1.09 (0.54-2.20)	0.81
Hypoglycaemia (All)	402	387	36	120	11%	40%	0.23 (0.16-0.33)	<0.01
Hypoglycaemia (Moderate/Severe)	402	387	8	52	2%	16%	0.13 (0.06-0.28)	<0.01
Hypoglycaemia (Severe)	24 events total across all 4 subgroups with both therapies - 21 SU, 3 TZD							
Non-obese females								
Oedema	203	166	31	12	19%	9%	2.07 (1.06-4.03)	0.03
Oedema (Moderate/Severe)	203	166	10	4	6%	3%	1.94 (0.61-6.19)	0.26
Fracture	208	174	19	4	18%	3%	3.42 (1.16-10.07)	0.03
Hypoglycaemia (All)	208	174	20	64	13%	52%	0.20 (0.12-0.33)	<0.01
Hypoglycaemia (Moderate/Severe)	208	174	6	34	3%	26%	0.13 (0.05-0.31)	<0.01
Hypoglycaemia (Severe)	24 events total across all 4 subgroups with both therapies - 21 SU, 3 TZD							
Obese females								
Oedema	370	352	78	46	29%	20%	1.36 (0.94-1.96)	0.10
Oedema (Moderate/Severe)	370	352	32	19	12%	11%	1.30 (0.74-2.31)	0.36
Fracture	407	379	41	14	16%	9%	2.17 (1.18-3.98)	0.01
Hypoglycaemia (All)	407	379	50	137	15%	45%	0.26 (0.19-0.36)	<0.01
Hypoglycaemia (Moderate/Severe)	407	379	14	59	5%	19%	0.19 (0.10-0.33)	<0.01
Hypoglycaemia (Severe)	24 events total across all 4 subgroups with both therapies - 21 SU, 3 TZD							

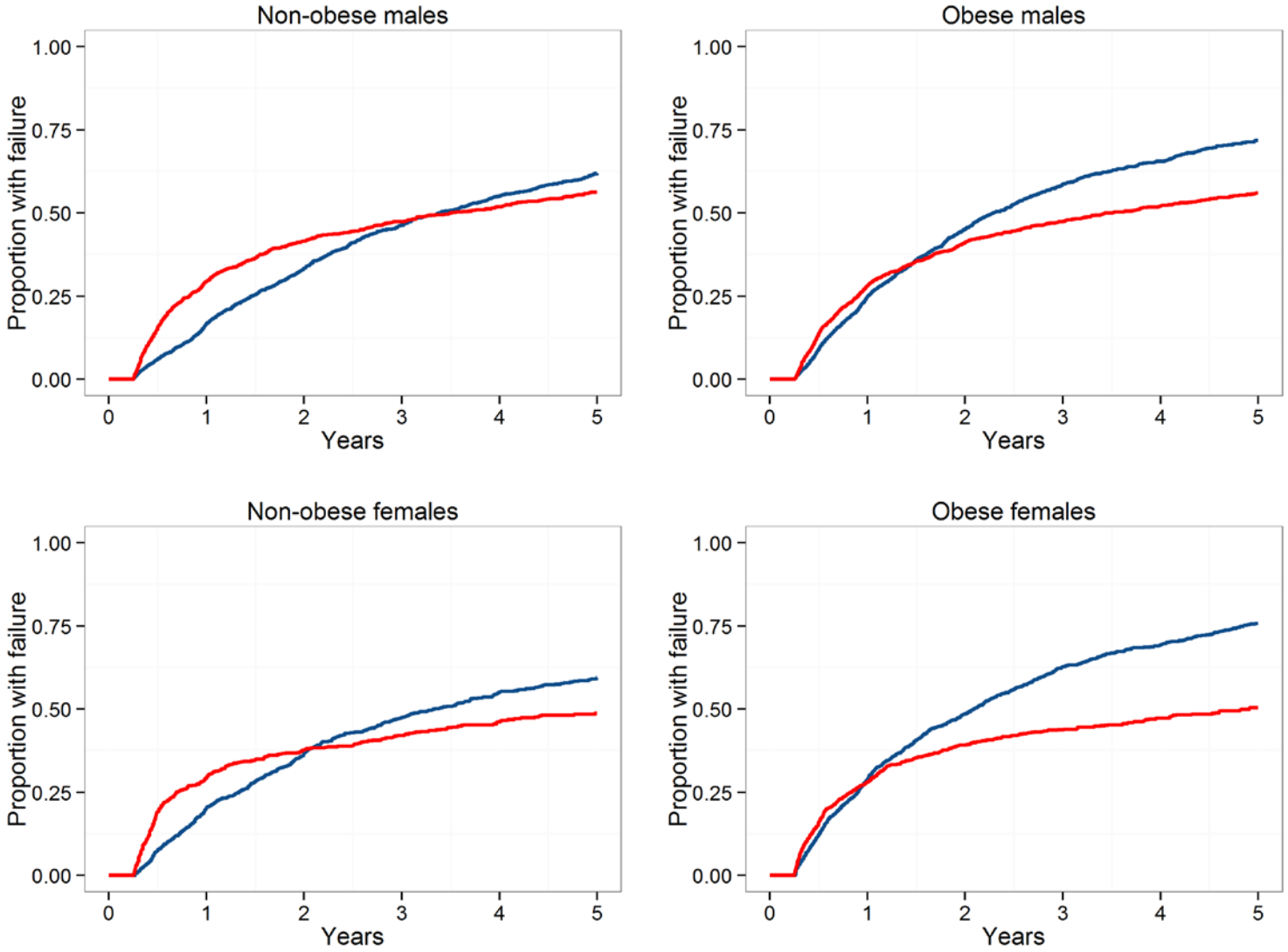
Supplementary Table 5: RECORD absolute and relative risk of side effects over 5 years with thiazolidinediones (TZD) and sulfonylureas (SU), by sex and obesity defined subgroup. Relative risks presented as hazard ratios (95% CI) for TZD compared to SU.

Side effect	No. of patients		No. of events		Absolute 5 year risk (%)		Hazard ratio*	p value*
	TZD	SU	TZD	SU	TZD	SU		
Non-obese males								
Oedema	240	228	13	9	7%	5%	1.59 (0.68-3.71)	0.29
Oedema (Moderate/Severe)	240	228	7	1	4%	1%	7.84 (0.96-63.7)	0.05
Fracture	240	228	14	6	9%	3%	2.66 (1.02-6.94)	0.04
Hypoglycaemia (All)	240	228	5	38	2%	18%	0.12 (0.05-0.31)	<0.01
Hypoglycaemia (Moderate/Severe)	240	228	2	16	1%	8%	0.12 (0.03-0.54)	<0.01
Hypoglycaemia (Severe)	10 events total across all 4 subgroups with both therapies - 10 SU, 0 TZD							
Obese males								
Oedema	361	356	48	21	17%	7%	2.61 (1.56-4.35)	<0.01
Oedema (Moderate/Severe)	361	356	24	6	9%	2%	4.45 (1.82-10.90)	<0.01
Fracture	361	356	12	14	5%	5%	0.94 (0.43-2.03)	0.88
Hypoglycaemia (All)	361	356	10	51	3%	16%	0.19 (0.10-0.38)	<0.01
Hypoglycaemia (Moderate/Severe)	361	356	5	18	2%	6%	0.29 (0.11-0.79)	0.015
Hypoglycaemia (Severe)	10 events total across all 4 subgroups with both therapies - 10 SU, 0 TZD							
Non-obese females								
Oedema	137	127	17	4	15%	4%	4.13 (1.39-12.2)	0.01
Oedema (Moderate/Severe)	137	127	3	1	3%	1%	2.77 (0.29-26.60)	0.38
Fracture	137	127	12	4	11%	3%	2.86 (0.92-8.88)	0.07
Hypoglycaemia (All)	137	127	3	26	3%	22%	0.10 (0.03-0.31)	<0.01
Hypoglycaemia (Moderate/Severe)	137	127	4	10	4%	9%	0.36 (0.11-1.3)	0.08
Hypoglycaemia (Severe)	10 events total across all 4 subgroups with both therapies - 10 SU, 0 TZD							
Obese females								
Oedema	379	394	75	20	23%	6%	4.37 (2.67-7.16)	<0.01
Oedema (Moderate/Severe)	379	394	28	6	9%	2%	5.16 (2.14-12.46)	<0.01
Fracture	379	394	36	19	12%	5%	2.12 (1.21-3.70)	<0.01
Hypoglycaemia (All)	379	394	14	73	4%	21%	0.19 (0.11-0.34)	<0.01
Hypoglycaemia (Moderate/Severe)	379	394	4	24	1%	7%	0.17 (0.06-0.50)	<0.01
Hypoglycaemia (Severe)	10 events total across all 4 subgroups with both therapies - 10 SU, 0 TZD							

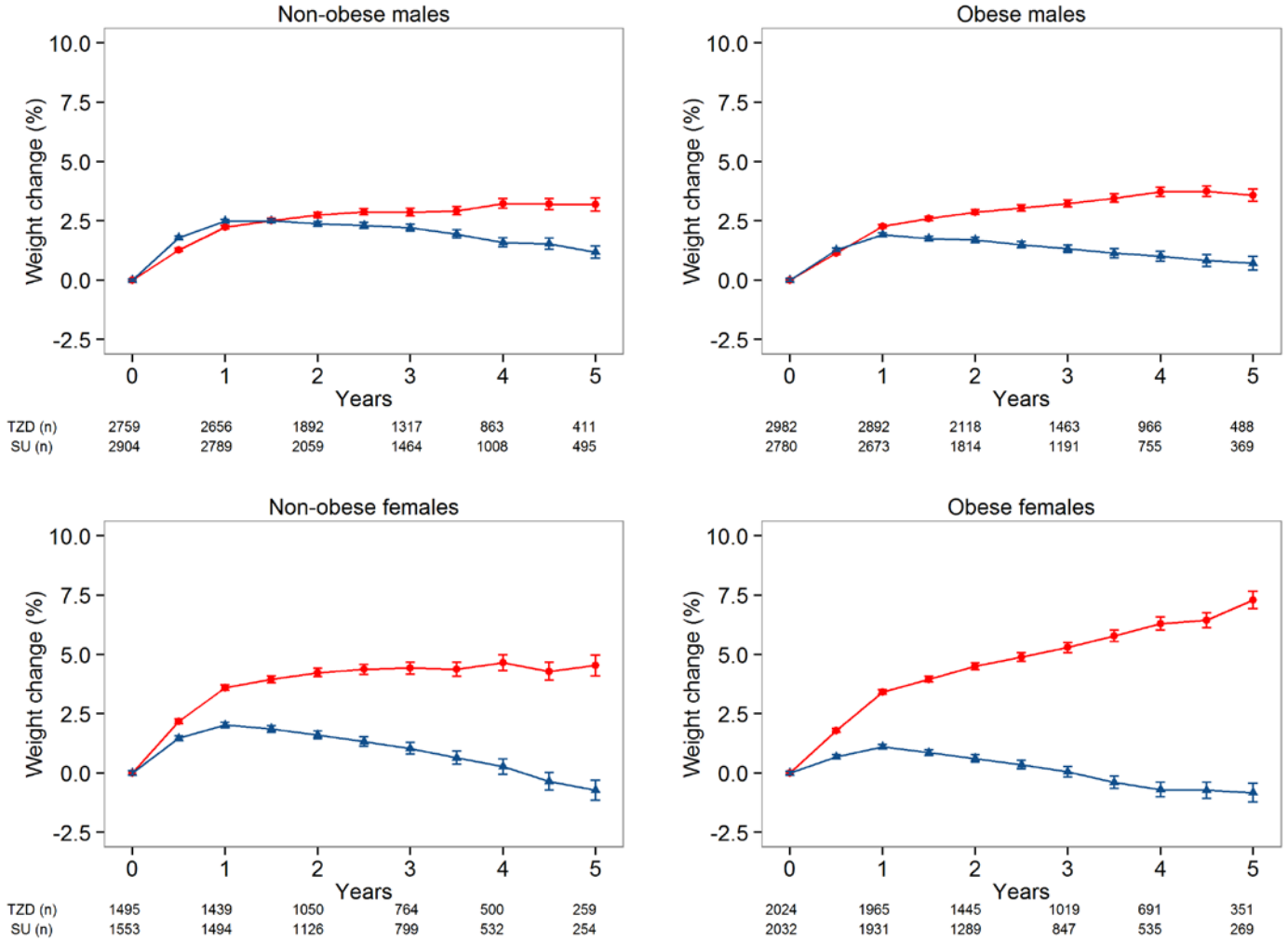
Supplementary Figure 11: CPRD HbA1c over 5 years with thiazolidinediones (red dots) and sulfonylureas (blue triangles), by sex and obesity defined subgroup. Data are presented as 3 monthly means ± standard error from mixed effects models, adjusted for baseline HbA1c. Number (n) per year presented below plots for each therapy and subgroup.



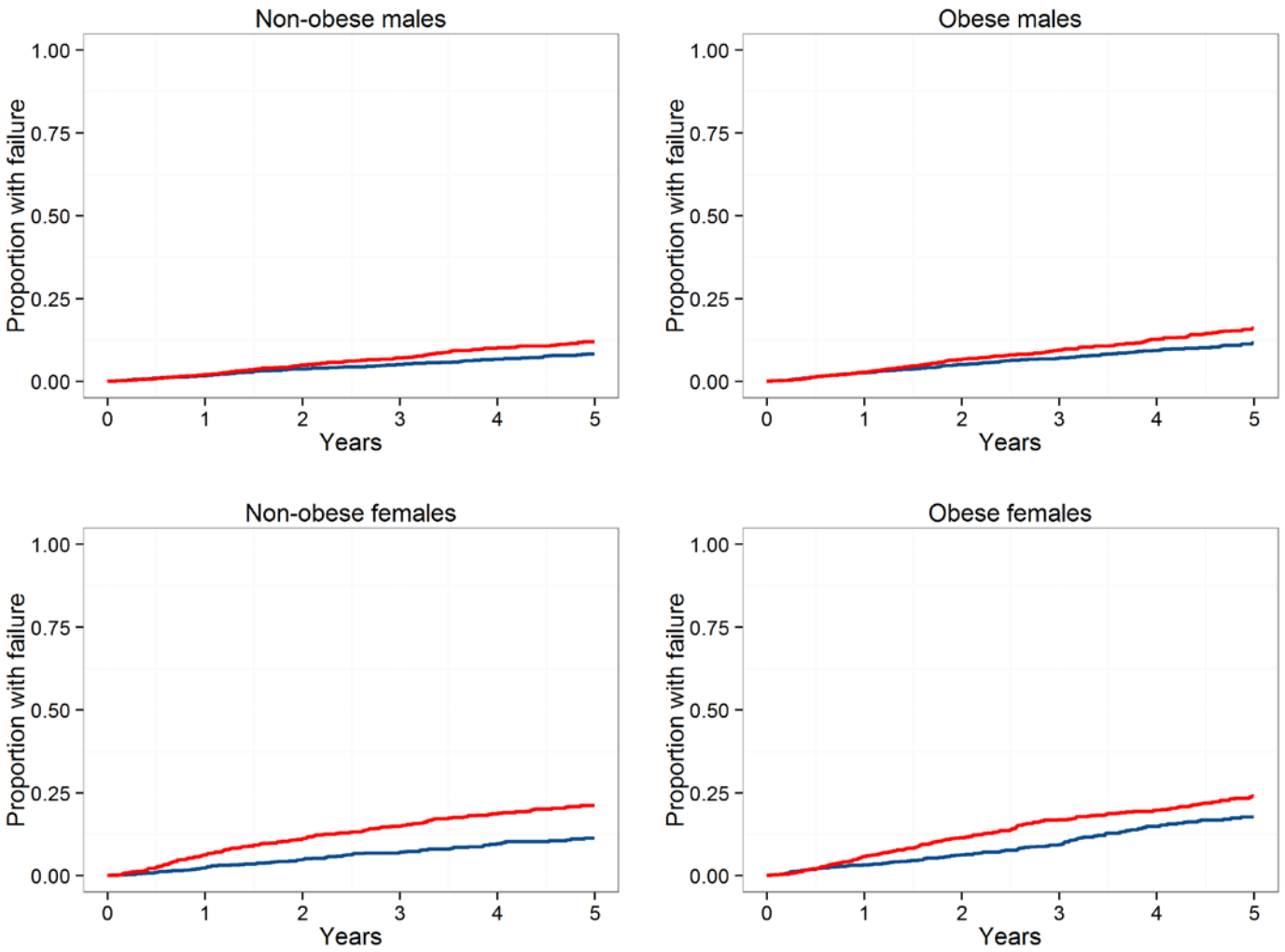
Supplementary Figure 12: CPRD Kaplan–Meier estimates of the cumulative incidence of failure of therapy over 5 years with thiazolidinediones (red) and sulfonylureas (blue). Failure defined as two consecutive HbA1cs >8.5% or one HbA1c >8.5% followed by an additional oral hypoglycaemic agent being added.



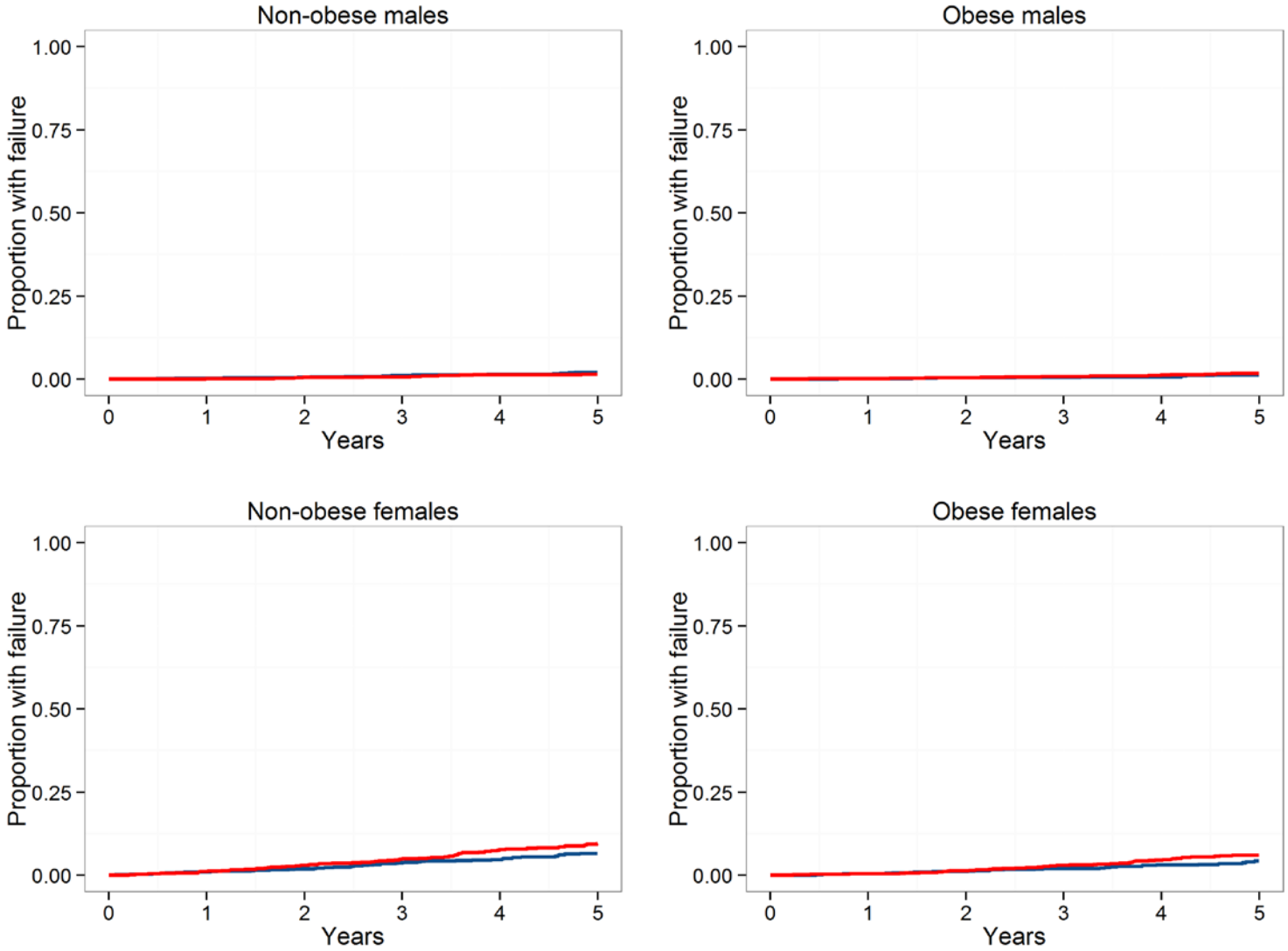
Supplementary Figure 13: CPRD percentage weight change from baseline over 5 years with thiazolidinediones (red dots) and sulfonylureas (blue triangles), by sex and obesity defined subgroup. Data are presented as 6 monthly means ± standard error from mixed effects models, adjusted for baseline HbA1c. Number (n) per year presented below plots for each therapy and subgroup.



Supplementary Figure 14: CPRD Kaplan–Meier estimates of the cumulative incidence of oedema over 5 years with thiazolidinediones (red) and sulfonylureas (blue)



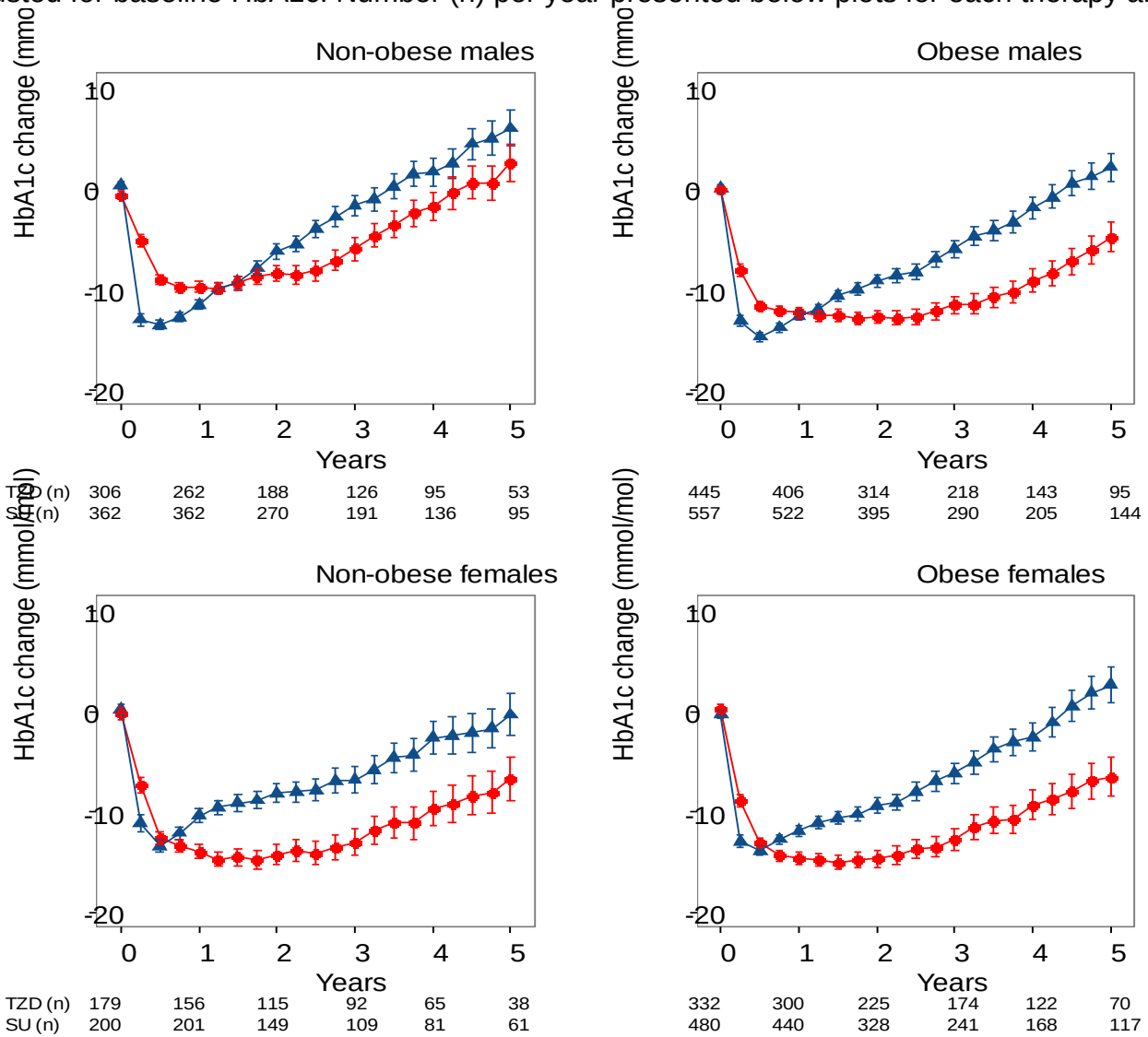
Supplementary Figure 15: CPRD Kaplan–Meier estimates of the cumulative incidence of fracture (any) over 5 years with thiazolidinediones (red) and sulfonylureas (blue)



Supplementary Table 6: GoDARTs population baseline characteristics, split by cohorts treated with thiazolidinediones (TZD) and sulfonylureas (SU). Data presented for the whole group and 4 subgroups defined by obesity (BMI>30kg/m^2) and sex.

	All		Non Obese Male		Non Obese Female		Obese Male		Obese Female	
TZD	**n**	**Mean(SD)**	**n**	**Mean(SD)**	**n**	**Mean(SD)**	**n**	**Mean(SD)**	**n**	**Mean(SD)**
Age diag (y)	719	55.6 (9.3)	176	56.7 (9.2)	97	59.9 (8.5)	267	52.9 (9.0)	174	56.1 (9.1)
Age (y)	719	63.7 (9.6)	176	65.9 (9.0)	97	69.0 (8.8)	267	60.7 (9.3)	174	63.3 (9.3)
Duration Diabetes (y)	719	8.2 (5.1)	176	9.2 (5.9)	97	9.2 (5.2)	267	7.8 (4.9)	174	7.2 (4.0)
BMI (kg/m^2)	714	32.2 (5.7)	176	27.3 (2.0)	97	26.8 (2.5)	267	34.9 (4.6)	174	36.0 (5.6)
Male (%)	719	62	176	100	97	0	267	100	174	0
Dose (weighted mean % max)	686	50 (23)	170	51 (25)	95	49 (22)	252	51 (23)	164	48 (22)
Adherence (%)	719	97 (5)	176	97 (5)	97	98 (3)	267	97 (5)	174	97 (5)
HbA1c (mmol/mol)	719	73.1 (12.5)	176	70.8 (12.0)	97	71.0 (11.6)	267	74.3 (12.5)	174	74.6 (13.0)
	All		**Non Obese Male**		**Non Obese Female**		**Obese Male**		**Obese Female**	
SU	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)
Age diag (y)	1258	58.8 (10.4)	350	59.8 (10.0)	219	64.0 (10.5)	336	56.1 (9.6)	285	57.2 (10.3)
Age (y)	1258	64.6 (10.2)	350	66.0 (9.9)	219	69.3 (9.8)	336	61.9 (9.6)	285	62.9 (10.3)
Duration Diabetes (y)	1258	5.8 (3.9)	350	6.2 (4.4)	219	5.4 (3.5)	336	5.8 (3.7)	285	5.7 (3.7)
BMI (kg/m^2)	1190	31.2 (5.5)	350	27.1 (2.1)	219	26.4 (2.5)	336	34.6 (4.1)	285	35.8 (4.8)
Male (%)	1258	57	350	100	219	0	336	100	285	0
Dose (weighted mean % max)	1167	29 (22)	330	26 (14)	202	24 (14)	307	30 (15)	268	37 (31)
Adherence (%)	1258	96 (6)	350	96 (6)	219	96 (6)	336	96 (5)	285	97 (5)
HbA1c (mmol/mol)	1258	70.9 (14.5)	350	68.8 (14.3)	219	69.0 (12.8)	336	71.4 (13.8)	285	72.9 (14.9)

Supplementary Figure 16: GoDARTs HbA1c over 5 years with thiazolidinediones (red dots) and sulfonylureas (blue triangles), by sex and obesity defined subgroup. Data are presented as 3 monthly means ± standard error from mixed effects models, adjusted for baseline HbA1c. Number (n) per year presented below plots for each therapy and subgroup.



CPRD – data supplement

Code lists for the CPRD analysis are provided in the published online data supplement, available from:
http://care.diabetesjournals.org/highwire/filestream/55298/field_highwire_adjunct_files/0/DC180344SupplementaryData.pdf

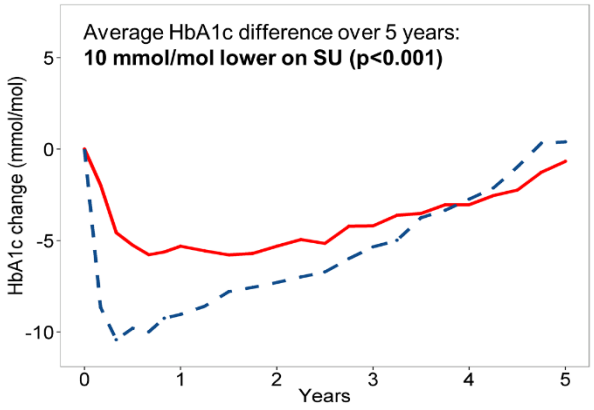
Subgroup Data summary

Summary for males BMI ≤30 on thiazolidinedione (red) and sulfonylurea (blue dotted/dashed). HbA1c and weight data from ADOPT, side effects from ADOPT and RECORD.

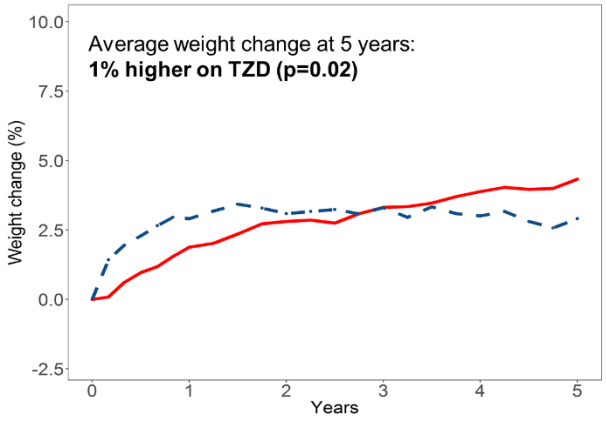
Males with a BMI ≤30

■ Thiazolidinedione ▒ Sulfonylurea

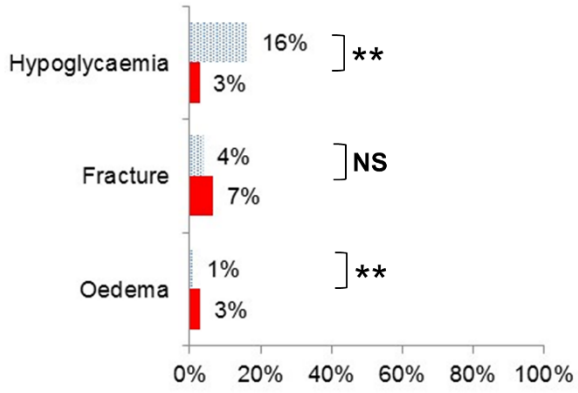
Average change in HbA1c from baseline



Average change in weight as a % of initial weight



Frequency of side effects at 5 years



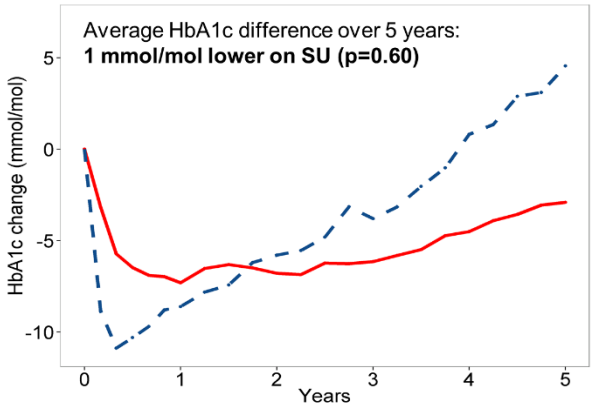
*** = p<0.05, ** = p <0.01, NS = no significant difference**

Summary for males BMI >30 on thiazolidinedione (red) and sulfonylurea (blue dotted/dashed). HbA1c and weight data from ADOPT, side effects from ADOPT and RECORD.

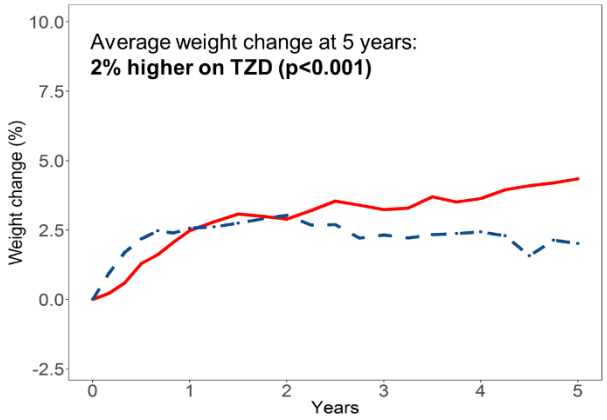
Males with a BMI >30

■ Thiazolidinedione ■ Sulfonylurea

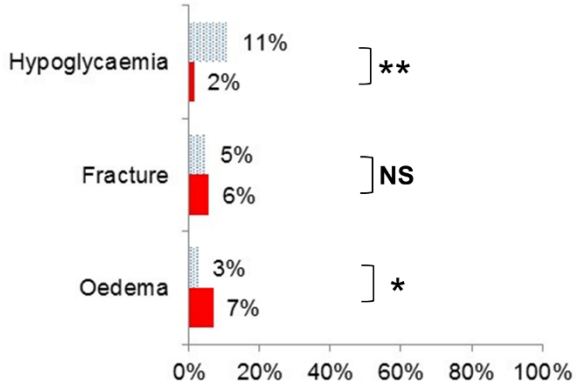
Average change in HbA1c from baseline



Average change in weight as a % of initial weight



Frequency of side effects at 5 years



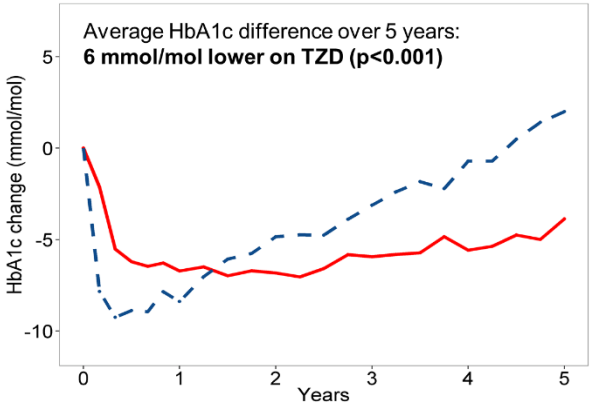
*** = p<0.05, ** = p <0.01, NS = no significant difference**

Summary for females BMI ≤30 on thiazolidinedione (red) and sulfonylurea (blue dotted/dashed). HbA1c and weight data from ADOPT, side effects from ADOPT and RECORD.

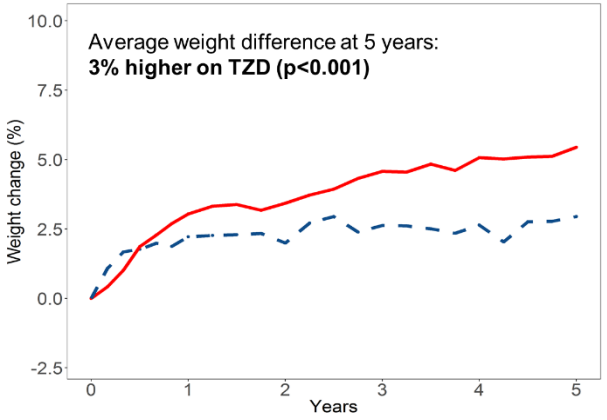
Females with a BMI ≤30

■ Thiazolidinedione ▒ Sulfonylurea

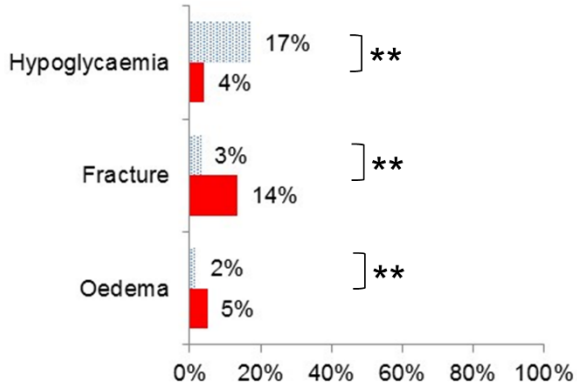
Average change in HbA1c from baseline



Average change in weight as a % of initial weight



Frequency of side effects at 5 years



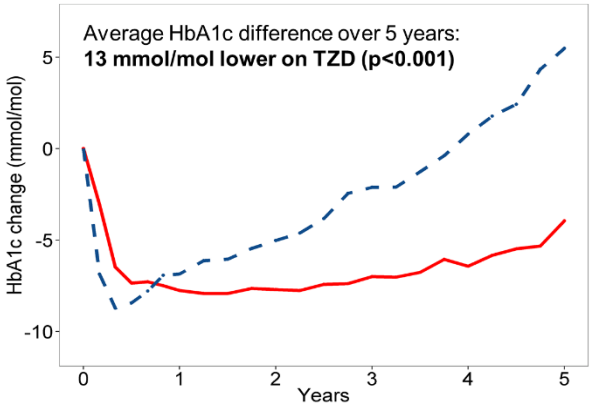
*** = p<0.05, ** = p <0.01, NS = no significant difference**

Summary for females BMI >30 on thiazolidinedione (red) and sulfonylurea (blue dotted/dashed). HbA1c and weight data from ADOPT, side effects from ADOPT and RECORD.

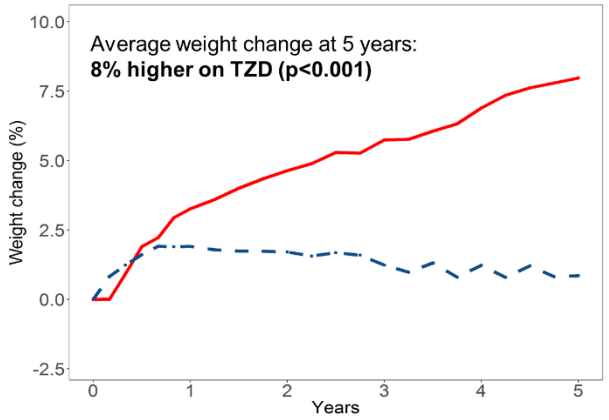
Females with a BMI >30

■ Thiazolidinedione ■ Sulfonylurea

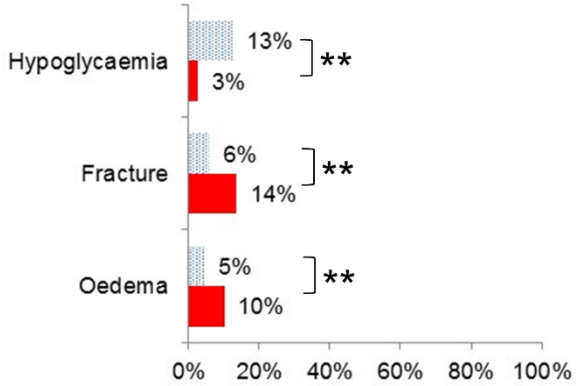
Average change in HbA1c from baseline



Average change in weight as a % of initial weight



Frequency of side effects at 5 years



*** = p<0.05, ** = p <0.01, NS = no significant difference**

Chapter 5

Evaluating associations between the benefits and risks of drug therapy in type 2 diabetes: A joint modelling approach

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Acknowledgments of co-authors and contributions to paper

William Henley, Andrew Hattersley, Beverley Shields, Angus Jones and I designed the study. I prepared and analysed the data, and drafted the manuscript. All authors provided support for the interpretation of results, critically revised the manuscript, and approved the final draft of the manuscript.

Abstract

Aim

Precision medicine drug therapy seeks to maximise efficacy and minimise harm for individual patients. This will be difficult if drug response and side-effects are positively associated, meaning patients likely to respond best are at increased risk of side-effects. We applied joint longitudinal-survival models to evaluate associations between drug response (longitudinal outcome) and risk of side-effects (survival outcome) for people initiating type 2 diabetes therapy.

Study Design and Setting

Participants were randomised to metformin, sulfonylurea or thiazolidinedione therapy in the ADOPT drug-efficacy trial (n=4,351). Joint models were parameterised for: 1) current HbA_{1c} response (change from baseline in HbA_{1c}); 2) cumulative HbA_{1c} response (total HbA_{1c} change).

Results

With metformin, greater HbA_{1c} response did not increase risk of gastrointestinal events (Hazard ratio (HR) per 1% absolute greater current response 0.82 (95% confidence interval 0.67,1.01); HR per 1% higher cumulative response 0.90 (0.81,1.00)). With sulfonylureas, greater current response was associated with increased risk of hypoglycaemia (HR 1.41 (1.04,1.91)). With thiazolidinediones, greater response was associated with increased risk of oedema (current HR 1.45 (1.05,2.01); cumulative 1.22 (1.07,1.38)) but not fracture.

Conclusion

Joint modelling provides a useful framework to evaluate the association between response to a drug and risk of developing side-effects. There may be

great potential for widespread application of joint modelling to evaluate the risks and benefits of both new and established medications.

Introduction

There is increasing interest in applying a precision medicine approach to select the most appropriate drug for a patient or subgroup of patients, in order to either improve response or to reduce side-effects.(1, 2) An important but overlooked question, particularly if side-effects are a result of the primary pharmacological effect of the drug, is whether the patients most likely to benefit are also at greatest risk of side-effects. Type 2 diabetes is an ideal candidate for precision medicine as there are many drug options to lower blood glucose (as measured by HbA_{1c}), but each drug has a different mechanism of action and specific side-effects. However, the association between HbA_{1c} response and side-effects is unknown for all drug options. If people likely to have a greater HbA_{1c} response to a specific drug are also at increased risk of side-effects this may limit the clinical utility of any precision approach to type 2 diabetes therapy.

To date, no robust framework has been proposed to evaluate the association between drug response and risk of side-effects. In type 2 diabetes, HbA_{1c} is measured repeatedly over time (a longitudinal process), whilst side-effect risk can be modelled as a time-to-event process. In this scenario, joint longitudinal-survival modelling is the preferred approach to evaluate the association between both processes.(3-6) Joint models attempt to capture the true, unobserved, longitudinal trajectory (in reality HbA_{1c} is measured intermittently and is subject to measurement error from random noise and biological variation). This means joint models can reduce bias and improve efficiency compared with simpler approaches.(5, 7) Joint models have been applied in many diseases including recently in type 1 diabetes (autoantibodies and time to disease onset),(8-11) but not to our knowledge in type 2 diabetes, or more

broadly to evaluate the association between drug response and risk of side-effects.

In this study we applied joint modelling to evaluate the association between drug response and risk of established side-effects for 3 widely used type 2 diabetes drugs, and thus further evaluate the potential for precision drug therapy in type 2 diabetes.

Material and Methods

Overview

Our aim was to understand whether the degree of glycaemic response to three common glucose-lowering drugs altered the risk of developing a side-effect. To answer this question we examined the association between two outcomes: 1) HbA_{1c} response (as measured by change from baseline in HbA_{1c}) and 2) risk of developing a side-effect (gastro-intestinal (GI) events, hypoglycaemia, oedema and fracture).

Setting and design

We used individual participant level data from the ADOPT randomised trial,(12) accessed through Clinical Trial Data Transparency Portal under approval from GSK (Proposal-930).(13) ADOPT was a prospective head-to-head drug trial including treatment-naïve participants with type 2 diabetes who were randomised to Metformin (MFN), the sulfonylurea (SU) glyburide or the thiazolidinedione (TZD) rosiglitazone (n=4,351 participants). The aim of ADOPT was to evaluate the long-term efficacy of the TZD compared to SU and MFN and the primary outcome was time to therapy failure (confirmed fasting plasma glucose ≥180 mg/dl). Study visits were every 2 months in year 1, then every 3

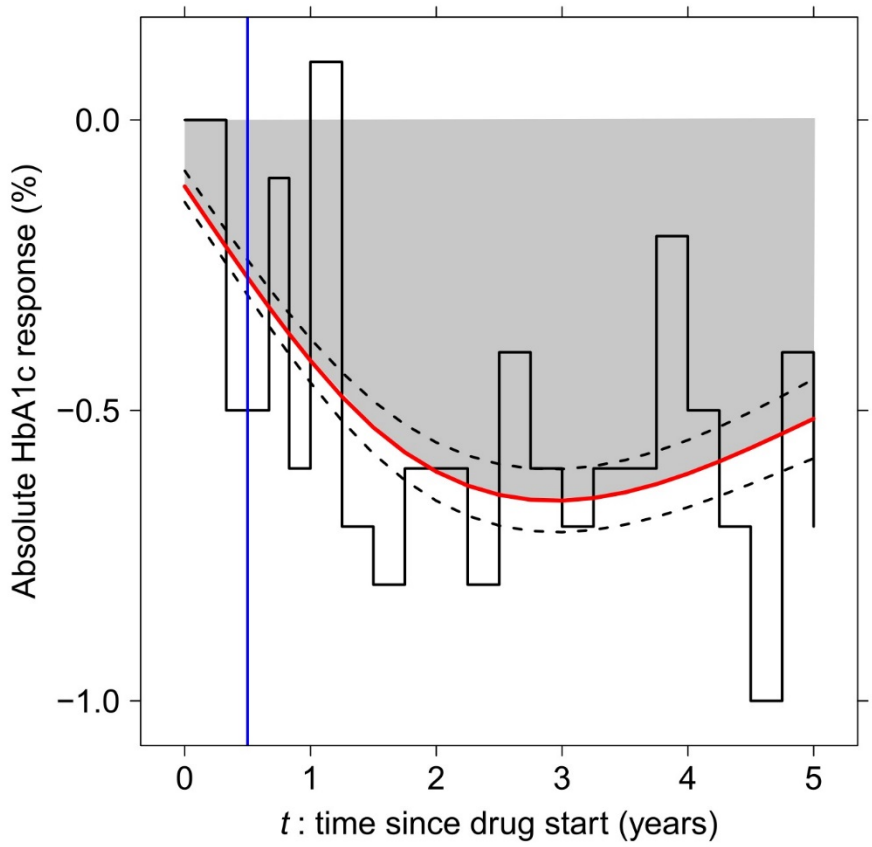
months up to 5 years. Clinically determined adverse events were recorded at each study visit, including records of GI events, hypoglycaemia, oedema and fracture. Biomarkers including HbA_{1c} were recorded at each visit. ADOPT participants in the intention to treat population with a valid baseline HbA_{1c} were eligible for our study. Participants were censored if they reached the trial primary endpoint of glycaemic failure, trial-recorded study withdrawal, or at 5 years after starting therapy as in the ADOPT main analysis.

Study outcomes

Our time-to-event outcomes were the first occurrence of 4 established drug-specific side-effects, over a 5 year period. For MFN the outcome of interest was a GI event, for SU it was a hypoglycaemia event (participant self-reported) and for TZD we evaluated oedema events and bone fractures.(12) Each drug and side-effect was analysed separately. We excluded participants s with a pre-trial history of oedema from the oedema analysis (6% of participants), but pre-trial hypoglycaemia, gastro-intestinal and fracture records were not available to do the same for other side-effects. Due to the high number of GI events we repeated the GI analysis restricted to only moderate/severe and severe events as sensitivity analysis. The longitudinal outcome of interest was HbA_{1c} response as measured by change from baseline in HbA_{1c} (HbA_{1c} at each study visit (%) – baseline HbA_{1c} (%)). Throughout HbA_{1c} percentages refer to absolute values rather than percentage changes. To test the specificity of our findings we repeated the analysis for each side-effect for the other drugs.

Figure 1: Approaches to estimating HbA_{1c} (%) response

Model 1: estimate current HbA_{1c} response using a joint model (red line with black dotted 95% confidence intervals).
Model 2: estimate cumulative HbA_{1c} response using a joint model (grey shaded area).
Model 3: carry forward the most recently observed value of HbA_{1c} response until the next measurement (LOCF approach, black step function).
Model 4: take the observed HbA_{1c} response at a single time point of 6 months (blue line).



Statistical analysis

We used a joint model with two parameterisations (Models 1-2) and two standard time-to-event models (Models 3-4), for comparison, to evaluate the association between HbA_{1c} response and the risk of developing a side-effect. A fundamental difference between each model was in the method to estimate HbA_{1c} response, as illustrated in Figure 1. Each side-effect was evaluated separately and the same modelling approach was applied for each side-effect. Participants were followed-up for up to five years from randomisation. As we

were assessing the association between side-effects and response, all participants required at least one pre-side-effect HbA_{1c} measure (meaning 4% of participants with very early side-effects were excluded from oedema analysis, 3% fracture, 20% hypoglycaemia, 12% GI). All models were adjusted for baseline HbA_{1c}.(14) Model setups were as follows:

Joint longitudinal-survival models

We used a maximum likelihood joint longitudinal-survival model to simultaneously assess the association between HbA_{1c} response (longitudinal process) and the risk of developing a side-effect (survival process). The joint model consisted of a two parts: a longitudinal submodel and a survival submodel linked through shared subject-specific random effects.(6)

In the general survival submodel, the hazard for individual i ($h_i(t)$) can be represented as:

$$h_i(t) = h_0(t)\exp(w_i^T\gamma + \alpha m_i(t)),$$

where $h_0(t)$ is the baseline hazard, w_i are baseline covariates, γ are regression coefficients, $m_i(t)$ is the "true, unobserved" longitudinal biomarker (estimated from the longitudinal submodel) and α quantifies the association between the longitudinal biomarker and the time-to-event process.(6)

We derived $m_i(t)$ from the observed HbA_{1c} response data using a linear mixed effects model with a non-linear term for time (as HbA_{1c} response is typically non-linear):

$$y_i(t) = m_i(t) + \epsilon_i(t)$$

$$= \beta_0 + \beta_1 N(t_i)_1 + \beta_2 N(t_i)_2 + \beta_3 \text{Baseline HbA1c} + b_{i0} + b_{i1} N(t_i)_1 + b_{i2} N(t_i)_2 + \epsilon_i(t),$$

where y_i is the observed HbA$_{1c}$ change from baseline and m_i the "true", unobserved HbA$_{1c}$ change from baseline. $N(t_i)_1$ and $N(t_i)_2$ denote the basis for a non-linear natural cubic spline of time with 1 internal knot at the 50th percentile of follow-up time (included in both the fixed and random effect parts of the longitudinal HbA$_{1c}$ submodel), b_i is a vector of subject specific random effects, $b_i \sim N(0, \widetilde{D})$ where $\widetilde{D}$ is the unstructured covariance matrix of random effects, ϵ_i is the vector of residuals, and $\epsilon_i \sim N(0, \sigma^2)$ where σ^2 is the covariance matrix of the residuals.(6) For models of hypoglycaemia with metformin and oedema with sulfonylureas we used a linear term for the random effect of time to achieve model convergence.

Model 1: Joint model current value (JMcv). To assess the association between the current value of HbA$_{1c}$ response and risk of side-effects (the standard formulation of the joint model) we incorporated m_i from the longitudinal submodel as a time-dependent covariate in the survival submodel:

$$h_i(t) = h_0(t)\exp\{\gamma_0 \text{Baseline HbA1c} + \alpha m_i(t)\}$$

Model 2: Joint model cumulative HbA$_{1c}$ *(JMcum).* To evaluate whether the risk of side-effects was associated with total rather than current HbA$_{1c}$ response we specified a second formulation of the joint model to assess the association between cumulative HbA$_{1c}$ response (total HbA$_{1c}$ response estimated as area-under-the-curve) and risk of side-effects, by including $\int_0^t m_i(s)\, ds\}$, the integral of the longitudinal HbA$_{1c}$ response trajectory up to time *t*, in the time-to-event submodel:(6, 15)

$$h_i(t) = h_0(t)\exp\{\gamma_0 \text{Baseline HbA1c} + \alpha \int_0^t m_i(s)\, ds\}$$

For models 1 and 2 we used a B-spline with 5 internal knots to flexibly model the baseline hazard function. We examined the fit of submodels using residual plots. Models 1 and 2 were fitted using the JM package in R.(16)

Model 3: Last-observation-carried-forward analysis (LOCF). We included observed HbA_{1c} response (HbA_{1c} at time *t* – baseline HbA_{1c}) as a time-dependent covariate in a Cox proportional hazards model. This approach does not correct for measurement error and assumes HbA_{1c} response is constant between measurements. Hazard ratios represent the increased risk of a side-effect for a 1-unit (%) absolute increase in the most recent value of HbA_{1c} change from baseline at time *t*.

Model 4: single estimate of HbA_{1c} response at 6 months (6mR). We evaluated the association between HbA_{1c} response at six months and subsequent risk of developing a side-effect. In this two-stage approach we first estimated a single estimate of HbA_{1c} response as a change score at 6 months. In the second stage we used this estimate as the exposure in a Cox hazards survival model with delayed entry to 6 months. Participants who developed a side-effect prior to 6 months or had no HbA_{1c} record at 6 months were excluded from this analysis (Supplementary Table 4).

Ethics approval

Data for the ADOPT trial were accessed through the Clinical Trial Data Transparency Portal, with study approval from GlaxoSmithKline (Proposal 930).

Results

The most common side-effects were GI side-effects with metformin (37%), followed by hypoglycaemia with sulfonylurea therapy (26%). Thiazolidinedione side-effects were less common (oedema 13%, fracture 7%, Table 1). Median follow-up was greater than 2.5 years in each cohort. For other participant characteristics see Supplementary table 1. Each side-effect occurred more frequently on these therapies than on the comparator drugs (Supplementary table 2).

Table 1: Participant numbers and study follow-up for each primary drug:side-effect cohort (Models 1-3). Data are median (IQR) unless stated. See Supplementary table 4 for participants included in Model 4.

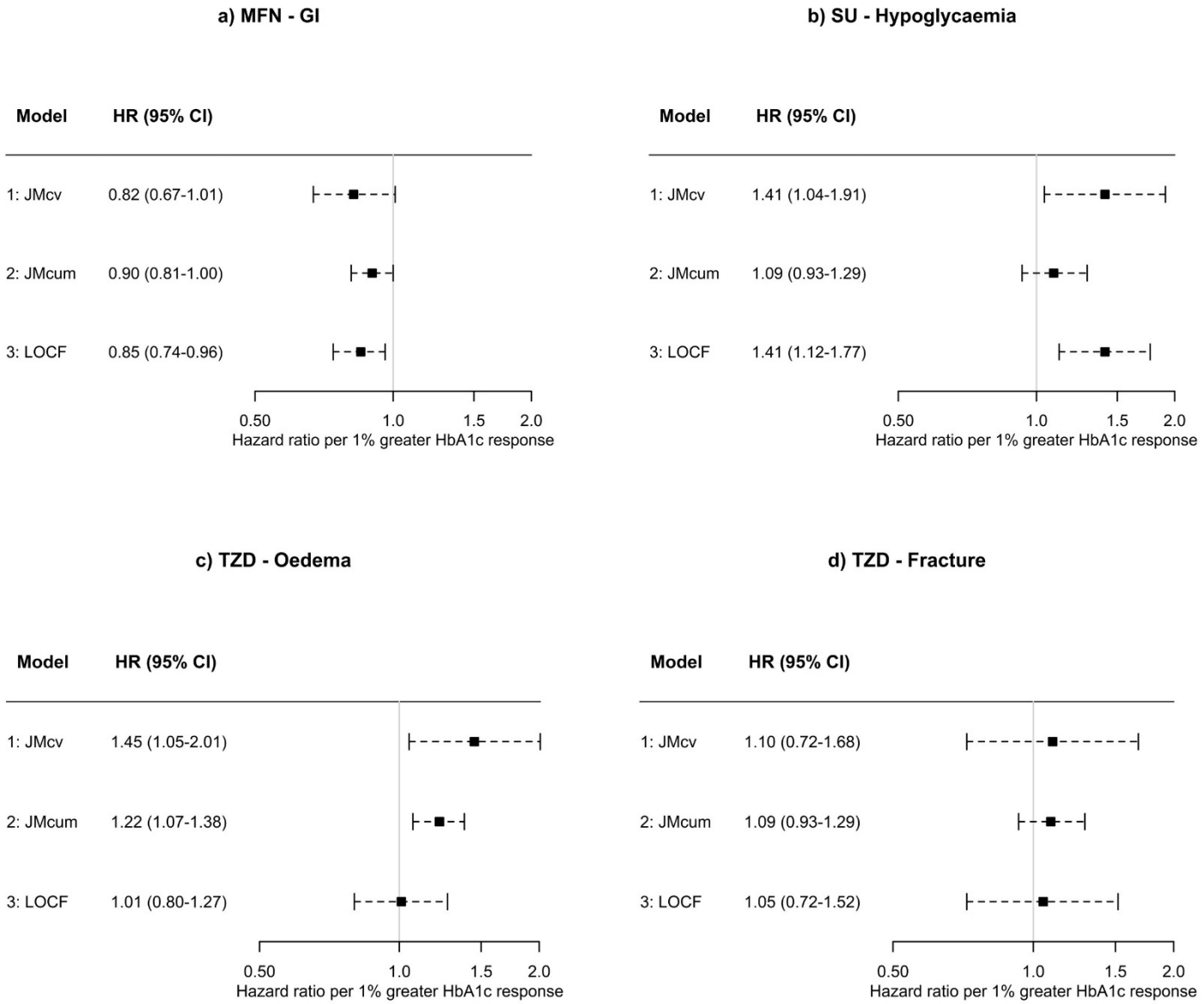
	Metformin - GI	SU - Hypo	TZD - Oedema	TZD - Fracture
No. of participants	1200	1052	1241	1311
No. of events (%)	440 (37%)	270 (26%)	164 (13%)	88 (7%)
Baseline HbA_{1c} %	7.3 (6.7;7.9)	7.3 (6.7;7.9)	7.3 (6.7;7.9)	7.3 (6.7;7.9)
No. recorded HbA_{1c}	13 (6;19)	12 (5;19)	18 (9;20)	18 (10;21)
Study follow-up (years)	2.8 (1.0;4.2)	2.5 (0.9;4.2)	4.0 (1.8;4.7)	4.0 (2.1;4.7)

Joint-model associations between HbA_{1c} response and risk of side-effects

GI events. With metformin we found consistent evidence for an association between greater HbA_{1c} response and reduced risk of a GI side-effect (Figure 2a). We observed a similar association for moderate/severe GI events (20% of participants) and no association for severe GI events (3% of participants) (Supplementary table 3). We found no evidence of an association with thiazolidinediones and sulfonylureas (Table 2**,** Supplementary table 3).

Hypoglycaemia. With sulfonylureas we found greater current HbA_{1c} response was associated with an increased risk of hypoglycaemia (Model 1:JMcv, Figure

Figure 2: Hazard ratios for the association between HbA_{1c} response and risk of a drug-specific side-effect (Models 1-3). Hazard ratios (95% confidence intervals) represent the increase in risk of a side-effect for a 1% greater absolute HbA_{1c} response**.** A hazard ratio greater than 1 indicates an increased risk of a side-effect with greater HbA_{1c} response.



2b). We found no evidence for an association between the risk of hypoglycaemia and cumulative HbA_{1c} response (Model 2:JMcum). With thiazolidinedione therapy, although the absolute risk of hypoglycaemia was much lower than with sulfonylurea therapy (8% versus 26%, p<0;001), greater current and cumulative HbA_{1c} response were associated with an increased risk of hypoglycaemia. There was no evidence of an association between response and hypoglycaemia with metformin (Table 2).

Oedema: With thiazolidinediones, greater current (Model 1:JMcv) and cumulative (Model 2:JMcum) HbA_{1c} response were associated with an increased risk of oedema (Figure 2c). We found no evidence of an association between HbA_{1c} response and risk of oedema with metformin and sulfonylureas (Table 2).

Fracture: With thiazolidinediones we found no evidence for an association between HbA_{1c} response and the risk of a fracture (Figure 2d). There was also no evidence of an association with metformin and sulfonylureas (Table 2, Supplementary table 6).

Table 2: Hazard ratios for the Association between HbA_{1c} Response and Risk of Side-effects (Models 1-3). Hazard ratios (95% Confidence Intervals) represent the increase in risk of a side-effect for a 1% greater absolute HbA_{1c} response**.** A hazard ratio greater than 1 indicates an increased risk of a side-effect with greater HbA_{1c} response.

Side-effect	Model 1: JMcv	Model 2: JMcum	Model 3: LOCF
		MFN	
Gastrointestinal	0.82 (0.67, 1.01), *P*=0.06	0.90 (0.81, 1.00), *P*=0.06	0.85 (0.74, 0.96), *P*=0.01
Hypoglycaemia	1.01 (0.63, 1.62), *P*=0.96	1.22 (0.93, 1.60), *P*=0.15	1.19 (0.88, 1.60), *P*=0.25
Oedema	1.16 (0.70, 1.92), *P*=0.58	1.09 (0.88, 1.36), *P*=0.42	1.07 (0.74, 1.56), *P*=0.71
Fracture	0.83 (0.48, 1.44), *P*=0.51	1.00 (0.78, 1.27), *P*=0.98	0.98 (0.69, 1.39), *P*=0.92
		SU	
Gastrointestinal	0.88 (0.69, 1.11), *P*=0.28	1.03 (0.92, 1.17), *P*=0.58	0.90 (0.77, 1.05), *P*=0.19
Hypoglycaemia	1.41 (1.04, 1.91), *P*=0.03	1.09 (0.93, 1.29), *P*=0.28	1.41 (1.12, 1.77), *P*=0.003
Oedema	1.31 (0.85, 2.02), *P*=0.23	1.09 (0.87, 1.36), *P*=0.45	0.87 (0.67, 1.13), *P*=0.28
Fracture	1.16 (0.70, 1.92), *P*=0.58	1.09 (0.88, 1.36), *P*=0.42	1.00 (0.64, 1.58), *P*=0.68
		TZD	
Gastrointestinal	1.21 (0.94, 1.55), *P*=0.13	1.05 (0.93, 1.18), *P*=0.44	1.04 (0.87, 1.26), *P*=0.65
Hypoglycaemia	1.98 (1.25, 3.15), *P*=0.004	1.37 (1.11, 1.7), *P*=0.003	1.44 (0.98, 2.12), *P*=0.07
Oedema	1.45 (1.05, 2.01), *P*=0.03	1.22 (1.07, 1.38), *P*=0.003	1.01 (0.80, 1.27), *P*=0.94
Fracture	1.10 (0.72, 1.68), *P*=0.65	1.09 (0.93, 1.29), *P*=0.28	1.05 (0.72, 1.52), *P*=0.81

Associations using standard time-to-event approaches

Results using the last-observation-carried-forward approach (Model 3:LOCF) were generally consistent with those from the current value joint model (Model 1:JMcv) (Table 2, Figure 2). The exception was for thiazolidinediones and oedema, for which, in contrast to the joint model, we found no evidence of an association using the LOCF model. Using Model 4:6mR (where HbA_{1c} response was estimated from a single 6 month value) we found no evidence of any association between HbA_{1c} response and risk of side-effects except for gastrointestinal events with Metformin (hazard ratio per 1% absolute increase in 6 month HbA_{1c} response 0.74 (95% CI 0.60, 0.91, Supplementary Table 4-5).

Discussion

Our study shows joint modelling can be a useful approach for evaluating associations between the benefits and risks of drug therapy. Using joint models for longitudinal and time-to-event data we were able to show important differences in the associations between drug response and risk of established side-effects for three widely-used type 2 diabetes drugs. We also found differences in the association between each of current and cumulative drug response and risk of side-effects, suggesting underlying differences in the nature of associations for the different drugs. Our results have implications for any precision medicine approach to type 2 diabetes therapy. More generally, they highlight the potential for widespread application of joint longitudinal-survival modelling to evaluate the benefits and risks of both new and established medications.

Advantages and disadvantages of joint models to evaluate the association between drug response and risk of side-effects

We found a key advantage of joint modes to be their flexibility. Different specifications of the joint model gave important additional insight into the underlying nature of associations between HbA_{1c} response and side-effects. These insights fitted with what is known about the pharmacological action of the different drugs. Current, but not cumulative, HbA_{1c} response was associated with an increased risk of hypoglycaemia with sulfonylureas. This is expected as hypoglycaemia is a side-effect related to short term fluctuations in blood glucose, rather than long term exposure. In contrast, for oedema with thiazolidinediones, which is less likely to relate to short-term fluctuations in

blood glucose, we observed associations for both current and cumulative HbA_{1c} response.

We also found associations with joint models that were missed by simpler approaches. With oedema with thiazolidinedione therapy there was no association using the last-observation-carried-forward approach but a clear association using both specifications of the joint model. This is likely due to the reduced bias and increased efficiency of the joint model compared with the last-observation-carried-forward approach which does not correct for measurement error in the longitudinal HbA_{1c} response.(5, 7) In general, hazard ratios using the last-observation-carried-forward approach had the same direction of association but were attenuated compared with those obtained from the current value joint model, in keeping with previous comparisons.(4, 17) We found a single measure of HbA_{1c} at 6 months was insufficient to show evidence of an association between HbA_{1c} response and side-effects, with the exception of GI side-effects with metformin where the association was consistent with the joint model.

There are some settings where joint models may be more limited. ADOPT was a large randomised, double-blinded trial and in this dataset we found joint models to be useful to evaluate the association between response and relatively common side-effects. Increasingly, similar trial datasets are available for researchers to address secondary research questions.(13, 18) It may be more challenging to apply joint modelling in other datasets. In particular, the potential of recording bias should be considered if conducting similar studies in electronic health records, although greater sample size may offer the opportunity to study rarer side-effects. Testing the specificity of results to drugs known to cause the side-effect by comparison with ‘negative control’ drugs may be a useful starting

point. Joint models may also be harder to apply to study associations between drug response and acute or allergic side effects that occur immediately after starting therapy. This was apparent in our analysis, as although we included over 1000 participants for each drug, participants who developed an early side-effect prior to their on-therapy HbA_{1c} were excluded, and this is a particular limitation of our analysis of hypoglycaemia with sulfonylureas. Another limitation of the joint modelling framework applied in this study is the assumption of a fixed association between longitudinal HbA_{1c} and risk of each side effect. Whilst inspection of residual plots indicated this was an appropriate strategy, it is certainly plausible that associations could change with therapy duration, and incorporating duration of therapy as a time-varying effect within the joint modelling framework would be of considerable interest. Similarly, an extension of the joint modelling framework to robustly incorporate drug dose and drug adherence could yield further insight to complement the response:side-effect associations evaluated in this study. Evaluating the impact of dose is a particular challenge in trials of drug efficacy such as ADOPT, as participants could be both uptitrated based on reaching glycaemic thresholds and down-titrated if a randomised medication was poorly tolerated. Adherence was not fully captured for participants in ADOPT, and poor adherence may have attenuated the associations observed in this study, as poor adherence is likely to be associated with both lesser drug response and increased side-effects. Consideration of adherence will be especially important if similar studies are conducted using routine clinical data, where adherence is likely to be much lower than in clinical trials.

Implications for a precision medicine approach to type 2 diabetes therapy

Our findings for the different drugs have implications for any future precision medicine approach to type 2 diabetes therapy. Greater metformin drug response was not associated with an increased risk of gastro-intestinal side-effects and this suggests great potential to target therapy if individuals likely to have greater drug response can be robustly identified.(19) However, targeting sulfonylureas and thiazolidinediones to individuals may be difficult as good responders are likely to be at increased risk of, respectively, hypoglycaemia and oedema. Our findings highlight the vital importance of considering both differential drug response and risk of side-effects in precision medicine studies, and this has been overlooked in previous work.(20, 21)

Our findings do not however preclude a precision medicine approach for sulfonylureas and thiazolidinediones. Identification of characteristics associated with either, but not both, improved drug response and lower risk of side-effects may allow the targeting of these therapies. Furthermore, decisions on therapy should ultimately be informed by absolute rather than relative risks of benefit or harm.(1) For example, if people likely to respond well to a thiazolidinedione can be identified then a thiazolidinedione may still be an appropriate option for people whose absolute risk of developing a side-effect is sufficiently low.

Comparison with other studies

To our knowledge this is the evaluation of the association between HbA_{1c} response and risk of side-effects for any of the three drugs, except for hypoglycaemia with sulfonylureas. Our results for sulfonylureas are consistent with previous observational studies that have examined the association between hypoglycaemia and achieved on-therapy HbA_{1c} (rather than HbA_{1c}

response).(22, 23) In the ACCORD trial, participants with greatest HbA_{1c} response at 4 months had a reduced rather than increased risk of hypoglycaemia, although this can be explained by the fact that in ACCORD the participants with least initial response were more likely to be on Insulin, the therapy with by far the strongest association with hypoglycaemia.(24)

In this study we found an unexpected association between greater response to TZD therapy and increased risk of hypoglycaemia, but no evidence of an association with metformin response, which would have indicated a positive association between increased drug response and increased risk of hypoglycaemia was a more general characteristic of glucose-lowering therapy. This is an interesting finding and one for which there is not a clear biological explanation, and it would be of interest to examine whether the TZD association can be replicated in other datasets. The association between oedema and HbA_{1c} response with thiazolidinediones is not unexpected as the mechanisms underlying both glucose-lowering and fluid retention are both thought to relate to PPARy stimulation.(25) With metformin there is no clear biological reason for the association between greater HbA_{1c} response and a lower risk of gastro-intestinal events. One possible explanation is decreased drug adherence in people experiencing mild gastro-intestinal symptoms prior to the event being recorded.

Future work

There is great potential to apply joint modelling to evaluate the association between drug response and risk of side-effects for the other drug options in type 2 diabetes and to study drug therapy in other diseases. Our findings also suggest a potential application of joint modelling as an efficient tool for understanding the risk-benefit trade-off at the individual-level in drug

development.(26) For precision medicine, the joint models used in this study could be extended to explore clinical features and biomarkers associated with drug response, risk of side-effects, or both.(27, 28) Alternative model specifications, such as evaluation of the effect of HbA_{1c} response slope,(6) the weighting of cumulative HbA_{1c} effects by recency,(15) the incorporation of multiple longitudinal biomarkers,(29) or incorporation of time-varying drug effects, may provide further insight into the nature of associations between response and side-effects. Similarly, incorporation of robust dose adjustment within the joint modelling framework, for example testing weighted cumulative drug associations,(30, 31) could allow much greater understanding of the impact of different levels of drug exposure on both response and adverse events. These are areas of current methodological development; a general mathematical presentation of joint modelling for simultaneously evaluating risks and benefits of medication would be a useful next step.

Conclusions

Joint modelling is a useful and efficient method to evaluate associations between continuous drug response and time to side-effects. Our study suggests the potential for application of joint modelling in both drug development and precision medicine research to evaluate the benefits and risks of medications. In type 2 diabetes, any future precision approach to sulfonylurea and thiazolidinedione therapy should consider the likely increased risk of respectively, hypoglycaemia and oedema, if targeting these therapies at people likely to have the greatest drug response.

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Supplementary Material

Supplementary table 1: Participant baseline characteristics for all drug:side-effect cohorts (Models 1-3). Data are mean (SD) unless stated.

	MFN:GI	SU:HYPO	TZD:OEDEMA	TZD:FRAC
No. of participants	1206	1052	1198	1311
Baseline HbA1c (%)	7.3 (0.9)	7.3 (0.9)	7.3 (0.9)	7.3 (0.9)
Age at therapy (years)	57 (10)	57 (10)	56 (10)	56 (10)
Sex (% male)	61%	60%	56%	55%
Duration diabetes (years)	1.0 (1.0)	1.0 (1.0)	1.0 (0.9)	1.0 (1.0)
BMI (kg/m2)	32 (6)	32 (6)	31 (6)	31 (6)

Supplementary table 2: Patient outcomes and study follow-up for all drug:side-effect cohorts (Models 1-3).

	No. of participants	No. of events (%)	Mean (SD) study follow-up
Gastro-intestinal			
MFN	**1200**	**440 (37%)**	**2.8 (1.7)**
SU	1206	281 (23%)	2.8 (1.7)
TZD	1252	293 (23%)	3.1 (1.6)
Hypoglycaemia			
MFN	1286	119 (9%)	3.3 (1.6)
SU	**1052**	**270 (26%)**	**2.6 (1.7)**
TZD	1281	104 (8%)	3.3 (1.6)
Oedema			
MFN	1248	78 (6%)	3.4 (1.6)
SU	1198	91 (8%)	3.5 (1.6)
TZD	**1241**	**164 (13%)**	**3.3 (1.6)**
Fracture			
MFN	1320	53 (4%)	3.4 (1.6)
SU	1320	53 (4%)	3.4 (1.6)
TZD	**1311**	**88 (7%)**	**3.4 (1.6)**

Supplementary table 3: Hazard ratios for the association between HbA1c response and risk of gastrointestinal side-effects of all, moderate/severe and severe intensity (Models 1-3). Hazard ratios (95% Confidence Intervals) represent the increase in risk of a GI side-effect for a 1% greater absolute HbA1c response**.** A hazard ratio greater than 1 indicates an increased risk of a GI side-effect with greater HbA1c response.

	Model 1: JMcv	Model 2: JMcum	Model 3: LOCF
		MFN	
All	0.82 (0.67, 1.01), *P*=0.06	0.90 (0.81, 1.00), *P*=0.06	0.85 (0.74, 0.96), *P*=0.01
Moderate/Severe	0.73 (0.56, 0.95), *P*=0.02	0.89 (0.77, 1.03), *P*=0.10	0.76 (0.65, 0.89), *P*<0.001
Severe	1.28 (0.60, 2.74), *P*=0.53	1.04 (0.74, 1.48), *P*=0.80	0.98 (0.69, 1.40), *P*=0.91
		SU	
All	0.88 (0.69, 1.11), *P*=0.28	1.03 (0.92, 1.17), *P*=0.58	0.90 (0.77, 1.05), *P*=0.19
Moderate/Severe	0.85 (0.62, 1.17), *P*=0.32	0.91 (0.78, 1.07), *P*=0.25	0.91 (0.73, 1.14), *P*=0.43
Severe	1.07 (0.51, 2.22), *P*=0.87	0.96 (0.69, 1.34), *P*=0.81	0.87 (0.55, 1.36), *P*=0.54
		TZD	
All	1.21 (0.94, 1.55), *P*=0.13	1.05 (0.93, 1.18), *P*=0.44	1.04 (0.87, 1.26), *P*=0.65
Moderate/Severe	1.16 (0.75, 1.31), *P*=0.38	1.06 (0.90, 1.24), *P*=0.51	0.99 (0.75, 1.31), *P*=0.95
Severe	1.15 (0.53, 2.52), *P*=0.72	1.02 (0.73, 1.43), *P*=0.90	1.13 (0.67, 1.13), *P*=0.64

Supplementary table 4: Number of participants and side effect events for Model 4: 6 month response. Participants were included if they had a valid baseline HbA1c and a valid on-therapy HbA1c at 6 months, and had no record of the side effect of interest prior to the 6 month HbA1c.

Side-effect	No. of patients (No. of events)		
	MFN	SU	TZD
Gastro-intestinal	1025 (329)	1057 (212)	1114 (238)
Hypoglycaemia	1149 (78)	879 (162)	1156 (79)
Oedema	1145 (68)	1094 (73)	1129 (144)
Fracture	1210 (38)	1167 (34)	1200 (80)

Supplementary table 5: Hazard ratios for the association between HbA1c response and risk of side-effects for Model 4: 6m Response. Hazard ratios represent the increase in risk of a side-effect for a 1% greater absolute HbA1c response at 6 months**.** A hazard ratio greater than 1 indicates an increased risk of a side-effect with greater HbA1c response.

	Gastrointestinal	Hypoglycaemia	Oedema	Fracture
MFN	**0.74 (0.60-0.91), p<0.01**	1.21 (0.78-1.88), p=0.38	1.28 (2.11-2.93), p=1.29	0.82 (0.43-1.57), p=0.55
SU	0.86 (0.71-1.06), p=0.16	**1.04 (0.79-1.35), p=0.79**	0.94 (0.65-1.36), p=0.75	0.94 (0.55-1.63), p=0.84
TZD	1.24 (0.97-1.57), p=0.08	1.01 (0.67-1.53), p=0.95	**1.06 (0.78-1.43), p=0.72**	**1.20 (0.79-1.80), p=0.39**

Supplementary Table 6: Hazard ratios for the association between HbA1c response and risk of side-effects, adjusted for drug dose as a time-varying covariate (Models 1-3). Hazard ratios (95% Confidence Intervals) represent the increase in risk of a side-effect for a 1% greater absolute HbA1c response**.** A hazard ratio greater than 1 indicates an increased risk of a side-effect with greater HbA1c response. **Bold = p<0.05.**

Side-effect	Model 1: JMcv	Model 2: JMcum	Model 3: LOCF
		MFN	
Gastrointestinal	0.83 (0.67-1.02), p=0.08	0.93 (0.83-1.04), p=0.19	0.87 (0.76-0.99), p=0.04
Hypoglycaemia	0.90 (0.56-1.45), p=0.66	0.94 (0.70-1.25), p=0.65	1.21 (0.90-1.64), p=0.21
Oedema	1.05 (0.63-1.76), p=0.85	1.17 (0.94-1.46), p=0.17	1.04 (0.71-1.51), p=0.85
Fracture	0.79 (0.45-1.38), p=0.35	0.95 (0.74-1.22), p=0.40	0.99 (0.69-1.40), p=0.94
		SU	
Gastrointestinal	0.98 (0.76-1.26), p=0.86	1.00 (0.88-1.14), p=0.97	0.96 (0.82-1.14), p=0.67
Hypoglycaemia	1.48 (1.07-2.06), p=0.02	1.22 (1.04-1.44), p=0.01	1.46 (1.15-1.86), p<0.01
Oedema	1.54 (0.96-1.54), p=0.07	1.26 (1.01-1.56), p=0.04	0.92 (0.71-1.20), p=0.53
Fracture	1.05 (0.63-1.76), p=0.54	1.17 (0.94-1.46), p=0.17	1.09 (0.67-1.77), p=0.73
		TZD	
Gastrointestinal	1.11 (0.86-1.44), p=0.42	1.06 (0.94-1.19), p=0.37	1.00 (0.83-1.20), p=0.99
Hypoglycaemia	1.94 (1.22-3.10), p<0.01	1.68 (1.37-2.07), p<0.01	1.53 (1.03-2.29), p=0.04
Oedema	1.47 (1.05-2.07), p=0.02	1.26 (1.11-1.43), p<0.001	1.03 (0.81-1.31), p=0.82
Fracture	1.00 (0.65-1.55), p=0.99	1.17 (0.99-1.39), p=0.06	0.99 (0.68-1.44), p=0.96

Chapter 6

Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared to models based on simple clinical features: an evaluation using clinical trial data

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Acknowledgments of co-authors and contributions to paper

Andrew Hattersley and I designed the study. I prepared and analysed the data, and drafted the manuscript. All authors provided support for the interpretation of results, critically revised the manuscript, and approved the final draft of the manuscript.

Abstract

Background

Recent research using data-driven cluster analysis has proposed five subgroups of diabetes with differences in diabetes progression and risk of complications. We aimed to compare the clinical utility of this subgroup-based approach for predicting patient outcomes with an alternative strategy of developing models for each outcome using simple patient characteristics.

Methods

We identified clusters in the ADOPT (n=4,351) trial cohort using the cluster analysis reported by Ahlqvist and colleagues (Lancet Diabetes Endocrinology 2018;6:361-69). Differences between clusters in glycaemic and renal progression were evaluated, and contrasted with stratification using simple continuous clinical features (respectively, age at diagnosis and baseline renal function). We tested the performance of a strategy of selecting glucose-lowering therapy using clusters with one combining simple clinical features (sex, BMI, age at diagnosis, baseline HbA_{1c}) in an independent trial (RECORD (n=4,447)).

Findings

Clusters identified in trial data were similar to those described in the original study. Clusters showed differences in glycaemic progression, but a model with age at diagnosis alone explained a similar amount of variation in progression. We found differences in CKD incidence between clusters however baseline eGFR was a better predictor of time to CKD. Clusters differed in glycaemic response, with a particular benefit for cluster 3 (insulin-resistant) with

thiazolidinediones and cluster 5 (older) with sulfonylureas. However simple clinical features outperformed clusters to select therapy for individual patients.

Interpretation

The proposed data-driven clusters differ in diabetes progression and treatment response, but models based on simple continuous clinical features are more useful to stratify patients. This suggests precision medicine in type 2 diabetes is likely to have most clinical utility if based on an approach of using specific phenotypic measures to predict specific outcomes, rather than assigning individuals into subgroups.

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Introduction

Type 2 diabetes is a heterogeneous multifactorial condition, comprising 90-95% of all diabetes and affecting over 400 million people worldwide. There is currently great interest in better characterising the heterogeneity in type 2 diabetes, and in exploiting this heterogeneity to improve care and outcomes for individuals with type 2 diabetes.(1-3)

In a recent study, Ahlqvist and colleagues identified five replicable clusters of individuals with diabetes in Scandinavian registry data.(4) The smallest cluster was defined by the presence of glutamic acid decarboxylase (GAD) autoantibody positivity, regardless of other characteristics (Cluster 1: severe autoimmune diabetes (SAID)). Four 'type 2' like clusters were then characterised by the absence of GAD positivity and varying degrees of differences in age at diagnosis, and baseline measures of BMI, HbA_{1c}, and HOMA2 measured insulin resistance and beta-cell function. The four 'type 2' clusters were named as follows; Cluster 2: severe insulin deficient diabetes (SIDD); Cluster 3: severe insulin resistant diabetes (SIRD); Cluster 4: mild obesity-related diabetes (MOD); Cluster 5: mild age-related diabetes (MARD). Ahlqvist and colleagues then showed potentially clinically important differences in disease progression and risk of complications between the clusters in observational follow-up, most notably a striking increase in the risk of diabetic kidney disease in the cluster characterised by insulin resistance (Cluster 3: SIRD).

The key question for any subgroup analysis is its clinical utility, and in particular whether the proposed subgroups differ in response to therapy which could help inform treatment strategies.(2) Ahlqvist and colleagues suggested but did not demonstrate that the clusters could be useful to guide choice of therapy.(5) To

date the only stratified approaches in type 2 diabetes showing large differences in response between treatments have used subgroups defined by routine clinical measures such as sex and BMI.(6) A further key question, raised by van Smeden and colleagues in response to the original study, is whether assigning individuals to clusters has greater clinical utility for predicting outcomes than an approach that combines continuous clinical features to predict outcomes for individual patients.(7)

We aimed to establish the clinical utility of the clusters by analysing two large existing trial datasets of individuals randomised to metformin, sulfonylurea and thiazolidinediones therapy, ADOPT and RECORD.(8, 9) In contrast to the observational follow-up in the original study of Scandinavian registry data, these trial datasets provided protocol-driven, randomised follow-up to evaluate clinical outcomes and differences in response to therapy. We compared the utility of the data-driven clusters with simpler approaches based on routine clinical measures available in any diabetes clinic.

Methods

Study population

The primary study population comprised newly diagnosed, drug-naïve, individuals with type 2 diabetes participating in the ADOPT trial of glycaemic durability, randomised to metformin, sulfonylurea (glibenclamide) or thiazolidinedione (rosiglitazone) monotherapy up to five years (n=4,351).(8) Eligibility criteria at screening included: Age 30-75 years, fasting plasma glucose 7-13 mmol/l, no evidence of renal impairment (serum creatinine >114 μmol/l for males or >106 μmol/l for females). As a replication dataset we used the RECORD study (n=4,447), a cardiovascular outcomes trial in individuals with established type 2 diabetes (mean duration of diabetes 7 years) initiating

the same drug classes as ADOPT but as dual second-line therapy, for up to six-years.(9) Sulfonylurea type was based on local practice (glibenclamide[18%], gliclazide[30%], or glimepiride[52%]), rosiglitazone was the thiazolidinedione used. Eligibility criteria included: Age 40-75 years, BMI >25.0 kg/m², HbA_{1c} >7.0% and ≤9.0%, and no evidence of renal impairment (serum creatinine >130 µmol/l).

We followed individuals in both trials from randomisation until the earliest of: the primary outcome of the original trial; censor date, five years, or the occurrence of an outcome of interest. Full individual level trial data were accessed through Clinical Trial Data Transparency Portal (Proposal 930).

Measurements

We calculated HOMA2 measures of insulin resistance and beta-cell function using fasting C-peptide and fasting-glucose measures using the HOMA 2 calculator.(10) In ADOPT GAD antibody positivity (yes or no) was measured using a commercially available radioimmunoassay.(11) In RECORD all required measures except GAD were measured at baseline, we calculated HOMA2 measures using fasting insulin as fasting C-peptide was not available. Sex, age at diagnosis, baseline BMI and baseline HbA_{1c} comprised the other measures required for cluster analysis.

Definitions of study outcomes

Glycaemic progression

Glycaemic progression was defined as the change in HbA_{1c} from one year up to five years (HbA_{1c} at time *t* – HbA_{1c} at one year), thus allowing for an initial period of treatment response up to one year.

Kidney disease

Chronic kidney disease (CKD) was defined as progression from normal GFR (eGFR ≥60 ml/min per 1.73m²) to confirmed CKD Stage 3 (two consecutive measures of eGFR <60 ml/min per 1.73m²). eGFR was calculated using CKD-EPI; as a sensitivity analysis eGFR was also calculated using MDRD.(12) Measures of renal function were recorded at baseline, six months and annually. If progression was confirmed, the first of the two study visits was used to define CKD onset. Albuminuria was defined as progression from normal urinary albumin to creatinine ratio (UACR) (UACR <30 mg/g) to either microalbuminuria (UACR 30-300 mg/g) or macroalbuminuria (UACR ≥300 mg/g). Individuals with eGFR <60 and UACR ≥30 at their baseline visit were excluded from, respectively, the analysis of CKD and albuminuria outcomes.

Glycaemic response

HbA_{1c} was evaluated as achieved HbA_{1c} and as cumulative HbA_{1c} reduction at three years as measured by area-under-the-curve (3 year AUC HbA_{1c}). AUC HbA_{1c} is equivalent to the time-updated HbA_{1c} measure used in the UK Prospective Diabetes Study outcomes model.(13) Three years was chosen as the time point at which average AUC HbA_{1c} was approximately equal between the three drugs.(8) Other time points will tend to favour a specific therapy; early time points will favour sulfonylureas as these agents have greater short-term response, whilst later time points favour thiazolidinediones which have greater glycaemic durability.(8)

Statistical analysis

Cluster analysis

In ADOPT, we repeated the clustering approach of Ahlqvist and colleagues.(4) Males and females were clustered separately then pooled, continuous

measures were mean centred and standardised, and continuous measures >5 standard deviations from the mean were excluded. K-means clustering specifying four clusters was applied to the GAD-negative subset of individuals as K-means clustering does not incorporate binary variables; all GAD-positive individuals were manually assigned to a separate cluster.(4) The same R command (kmeansrun), number of runs (100) and measure of cluster stability (Jaccard coefficient >0.75 after 2000 bootstraps) were applied.(14) Once clusters were defined we assigned the same cluster names as in the original study, based on the distribution of cluster characteristics. In RECORD, we 1) assigned each individual to their ADOPT-derived cluster based on their Euclidean distance from each cluster centre; 2) repeated the cluster analysis to derive RECORD-specific clusters. As GAD was not available, all individuals in RECORD were assumed to be GAD-negative.

Glycaemic progression

In both trials, mean HbA_{1c} trajectories from randomisation up to five years for each cluster were first estimated using a repeated-measures mixed-effects model, including fixed effects for study visit, assigned cluster, and a study visit by cluster interaction. Patient-level random effects and an unstructured covariance matrix were specified for this and subsequent mixed-effects models. All individuals within a trial were pooled, regardless of randomised therapy. To estimate glycaemic progression by cluster the same model was then fitted but with HbA_{1c} change from one year as the outcome. We estimated the mean annual rate of glycaemic progression for each cluster by updating the cluster model to replace study visit with time as a linear covariate. Mean HbA_{1c} by age was estimated using the same model but a linear term for continuous age at diagnosis replacing the clusters. For each model we estimated the proportion of

variance explained (R^2) by the fixed effects, the AIC, and the adequacy index.(15, 16)

Kidney disease

We compared the cumulative incidence of CKD by cluster, using Kaplan-Meier plots and unadjusted and baseline eGFR (a continuous linear term) adjusted Cox proportional hazard models with cluster as a categorical variable. We estimated R^2 and the discrimination ability (Harrell's C-index) of the unadjusted cluster Cox model, compared with a Cox model with continuous baseline eGFR as a linear term.(16) We repeated the same analysis for time to a 30% decline in eGFR, and for time to albuminuria with and without adjustment for baseline UACR as a continuous linear term. We also compared continuous relative changes from baseline in eGFR and UACR progression over 0-5 years by cluster using a mixed-effects models with fixed effects for study visit, cluster, and study visit by cluster interaction.

Glycaemic response

We first evaluated whether HbA_{1c} response to the three drugs differed across the clusters in ADOPT. Average HbA_{1c} trajectories by drug were estimated up to three years for each cluster separately, using repeated-measures mixed-effects models with fixed effects for study visit, drug, visit by drug interaction and visit by baseline HbA_{1c} interaction. 3 year AUC HbA_{1c} was estimated for each drug in each cluster as the integral of the area under the mean HbA_{1c} trajectory using the trapezoidal rule.

Treatment selection based on HbA_{1c} – are clusters or clinical features more useful to guide therapy?

We evaluated whether clusters were more useful than simple clinical features to select a drug for individual patients based on predicted 3 year AUC HbA_{1c}.

Models to predict HbA_{1c} were developed in ADOPT using two strategies: A) using the clusters and B) using clinical features. For the clusters strategy we simply estimated HbA_{1c} response for each drug at the cluster level and applied this to all individuals within the cluster. This strategy treats individuals within a cluster as homogenous for treatment response to a particular drug. For the clinical features strategy we combined sex and linear terms for age at diagnosis, baseline BMI and baseline HbA_{1c} (the 4 routine clinical features informing the clusters) in a multivariable model to estimate HbA_{1c} response specific to each individual for each drug. The benefit of using each strategy developed in ADOPT to select treatment for individuals was then tested in an external trial population: RECORD.

1) Model development - ADOPT

Strategy A) clusters model: 3 year AUC HbA_{1c} for each drug was estimated at cluster level as detailed in the first step (Statistical analysis: Glycaemic response). Strategy B) clinical features model: 3 year AUC HbA_{1c}, as defined above, was estimated for each individual based on their precise clinical characteristics, using multivariable repeated-measures mixed-effects models for each drug. Each model had HbA_{1c} up to 3 years as the outcome with age at diagnosis, BMI, baseline HbA_{1c} and study visit by baseline HbA_{1c} interaction as continuous linear terms, and study visit and sex as fixed effects. Model performance for each strategy was assessed using R^2.

2) Assessment of the treatment selection strategy in independent data – RECORD

The purpose of a treatment selection model is to select the most effective therapies for individual patients, and therefore improve outcome at a population level, rather than to predict drug response accurately. This means the true test

of a treatment selection model is whether it can robustly identify individuals likely to benefit from particular therapies.(17) Standard model performance metrics test the ability of a model to predict the outcome, and are therefore of limited use in this context.(17, 18)

We therefore applied the following steps to test the effectiveness of each treatment selection strategy. For each individual in RECORD, we applied the models developed in ADOPT to obtain estimates of 3 year AUC HbA_{1c} on each drug. Under Strategy A) these predictions were according to the individual's assigned cluster (the same for all individuals within a cluster). Under Strategy B) predictions were at the individual level estimated from precise clinical features. For each strategy, we then applied a simple decision rule to assign individuals into two groups, one 'concordant' and one 'discordant'. Discordant individuals were those randomised to a drug with a predicted 3 mmol/mol higher 3 year AUC HbA_{1c} (i.e. less improvement in HbA_{1c}) than the drug predicted to be their best drug; all other individuals were defined as concordant.(19) The effectiveness of each treatment selection strategy was determined by the difference in 3 year AUC HbA_{1c} between the concordant and discordant groups. 3 year AUC HbA_{1c} by concordant/discordant group was estimated as previously described from a mixed-effects model with study visit, concordant/discordant group, baseline HbA_{1c}, study visit by concordant/discordant group interaction and visit by baseline HbA_{1c} interaction as fixed effects. We tested the sensitivity of results to the HbA_{1c} threshold used to define concordance by repeating the analysis at HbA_{1c} thresholds of 0, 1, 2 and 4 mmol/mol. All analyses were conducted using R version 3.4.1.

Cardiovascular outcomes

In RECORD we compared the time to the trial primary outcome, cardiovascular hospitalisation or cardiovascular death, by cluster using unadjusted and baseline age adjusted Cox proportional hazard models.

Assignment of clusters in ADOPT based on cluster centre coordinates from the Swedish ANDIS cohort

We assigned individuals in ADOPT to their ANDIS cluster based on their Euclidean distance from the cluster centres published by Ahlqvist and colleagues for the ANDIS cohort.(4) We then estimated glycaemic and renal progression and HbA_{1c} response for each ANDIS-derived cluster, and compared model performance of the ADOPT defined clusters and ANDIS clusters.

Role of the funding source

The funders had no role in the study design, collection, analysis, data interpretation or writing of the report. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

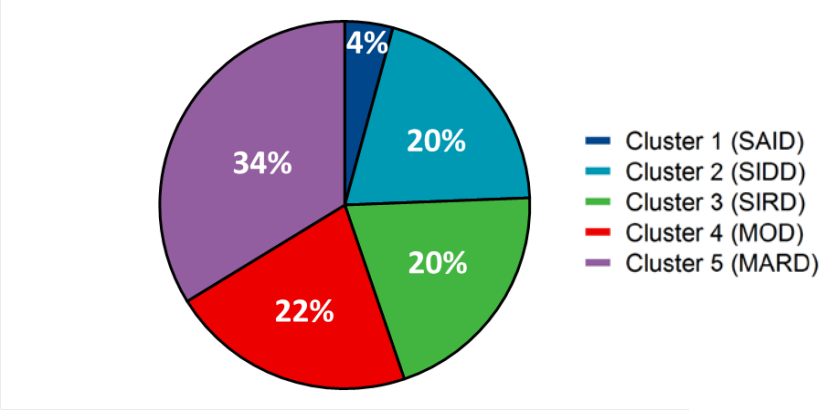
We found the clusters identified by Ahlqvist and colleagues were reproducible in trial populations. 4,003 individuals in ADOPT had valid baseline measures for cluster assignment. Of these, 3,802 were in the intention-to-treat population and so were eligible for analysis of patient outcomes. We found a clear pattern of differences between clusters in clinical characteristics (Figure 1A, Supplementary Tables 1, 3, 4), and were able to assign the same cluster names as Ahlqvist and colleagues (Figure 1B). Clusters were reasonably stable (Jaccard mean range: males 0.76-0.82; females 0.69-0.82). Cluster-centre coordinates are shown in Supplementary Table 2. In RECORD 4,148

individuals were eligible for cluster assignment (4,057 in intention-to-treat population). RECORD clusters were similar to the ADOPT clusters whether assigned from ADOPT or defined de-novo in RECORD (Supplementary Figure 1).

Average HbA_{1c} trajectories by cluster from randomisation to five years are shown in the Supplementary Figure 2. Glycaemic progression from one year differed by cluster in ADOPT (Figure 2A), with a higher rate of progression in Clusters 1 (SAID), 2 (SIDD) and 4 (MOD). In RECORD only Cluster 4 (MOD) had a higher rate of progression (Supplementary Figure 3). However, in both trials older age at diagnosis was associated with a lower rate of glycaemic progression (mean annual difference in rate of HbA_{1c} change per year increase in age at diagnosis: ADOPT -0.06 mmol/mol (95% confidence intervals -0.07 to -0.05; RECORD -0.05 mmol/mol (95%CI -0.06 to -0.04)) (Figure 2B, Supplementary Figure 3). Age at diagnosis explained a similar proportion of variation in progression to the clusters (ADOPT R^2=0.09 age at diagnosis, R^2=0.08 clusters; RECORD R^2=0.05 age at diagnosis, R^2=0.05 clusters). Other measures of model performance were also similar (Supplementary Table 5).

Figure 1: **Cluster distribution and cluster characteristics in ADOPT (n=4,003)**. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MOD=mild obesity-related diabetes. MARD=mild age-related diabetes. HOMA2-B=homoeostatic model assessment 2 estimates of β-cell function. HOMA2-IR=homoeostatic model assessment 2 estimates of insulin resistance.

(A) Distribution of ADOPT participants according to k-means clustering



(B) Distributions of HbA_{1c}, BMI, age at diagnosis, HOMA2-B, and HOMA2-IR at baseline for each cluster

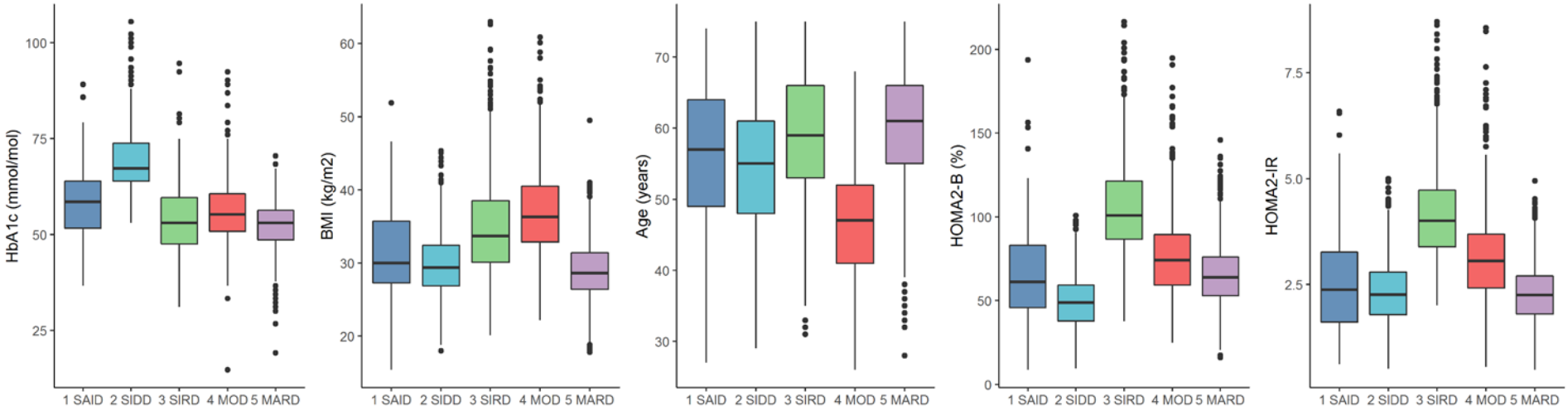
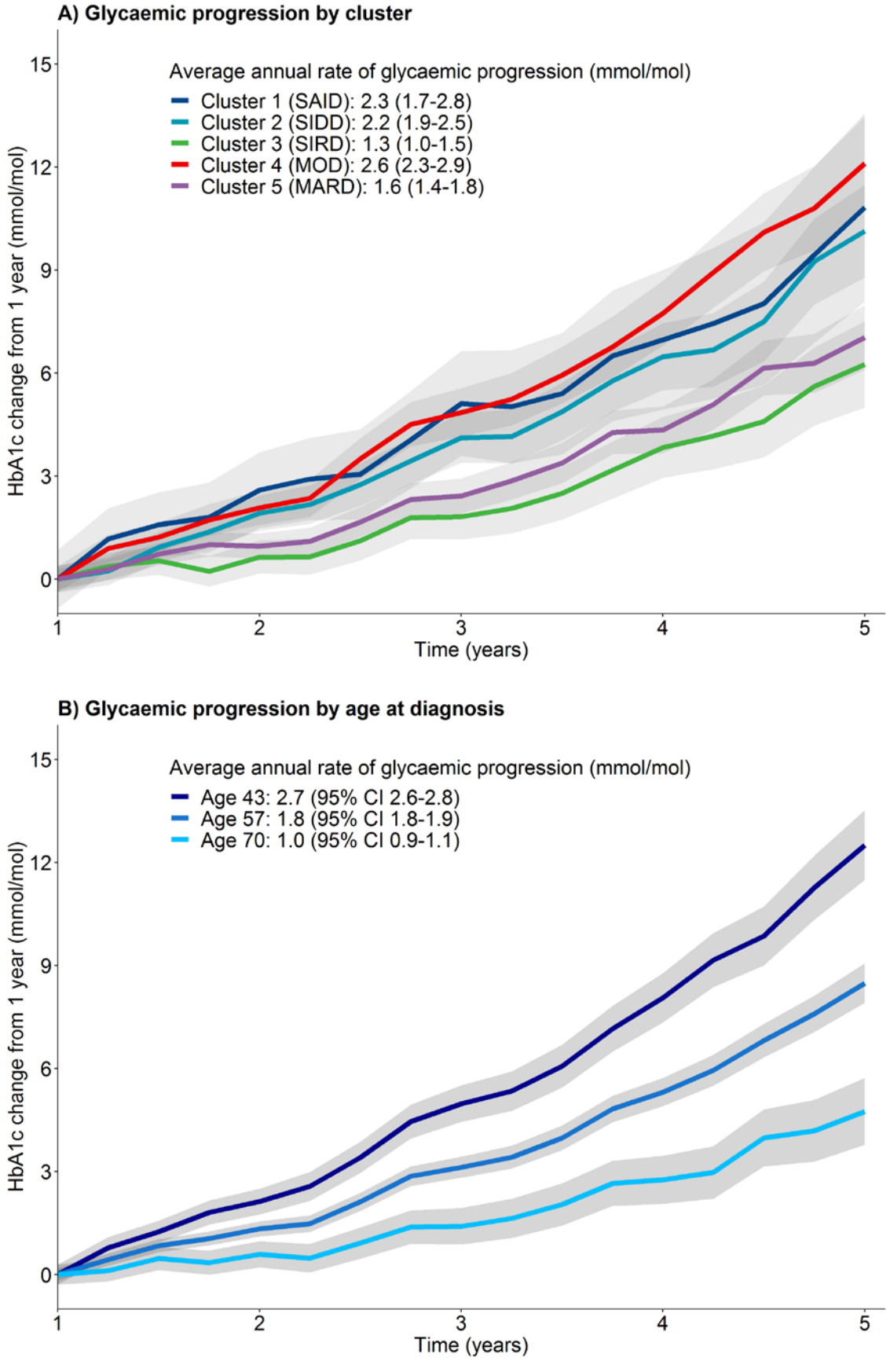


Figure 2: **Glycaemic progression by cluster in ADOPT from one to five years** A) HbA_{1c} change by cluster (n=3,016); B) HbA_{1c} change by age at diagnosis (10^{th}, 50^{th} and 90% percentile of ADOPT participants) (n=3,016). Data are estimates from repeated measures mixed-effects models.

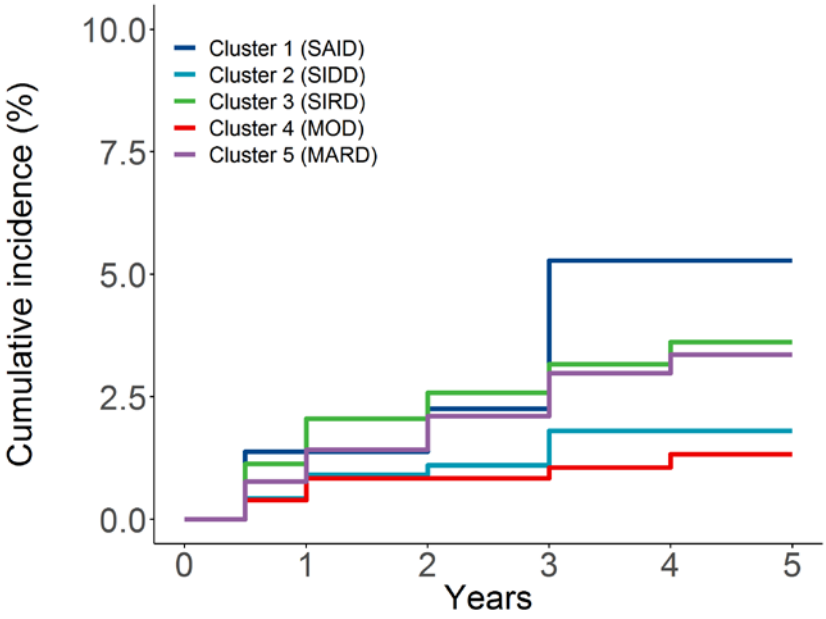


We found differences in the incidence of CKD between clusters after excluding patients with pre-existing CKD; clusters 1, 3 and 5 had the highest incidence of CKD (Figure 3A**,** Supplementary Figure 4). However, there were differences between the clusters in baseline renal function: the clusters with the highest incidence of CKD had the lowest eGFR (Supplementary Table 4). After adjustment for baseline eGFR there was no evidence of a difference in time to CKD across the clusters (Table 1, Supplementary Table 6). Results were similar using MDRD calculated eGFR (Supplementary Table 7). In ADOPT baseline eGFR explained a greater proportion of variation (R^2=0.18) and discrimination ability (C-statistic 0.90) than the clusters (R^2=0.01, C-statistic=0.58); this was similar to results in RECORD (baseline eGFR R^2=0.15, C-statistic 0.86; clusters R^2=0.01, C-statistic=0.57). Relative change from baseline in eGFR and time to 30% decline in eGFR did not differ by cluster (Supplementary Figures 5-6, Supplementary Table 8).

There was no clear pattern of difference between clusters in baseline UACR (Supplementary Table 4), in incidence of albuminuria (Figure 3B**,** Supplementary Figure 4), or in relative change in UACR (Supplementary Figure 7). After adjustment for baseline UACR time to albuminuria was shorter for cluster 3 (SIRD) versus cluster 2 (SIDD) in ADOPT, but not RECORD (Table 1, Supplementary Table 6). The clusters had no prediction and discrimination ability (ADOPT R^2=0.00, C-statistic=0.52; RECORD R^2=0.00, C-statistic=0.52), baseline UACR was a more useful measure (ADOPT R^2=0.12, C-statistic=0.74; RECORD R^2=0.10, C-statistic=0.73).

Figure 3: **Renal progression by cluster in ADOPT over five years.**

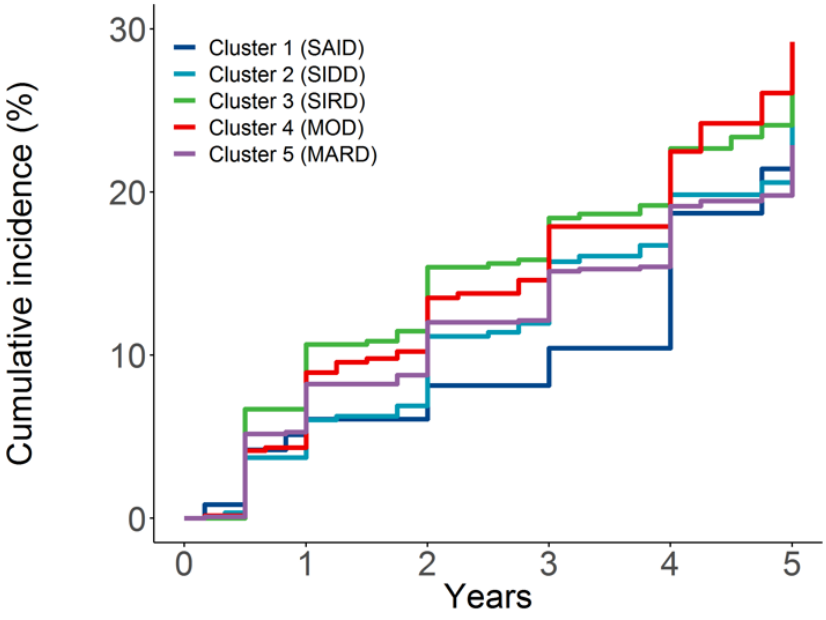
(A) Cumulative incidence of CKD Stage 3 (confirmed eGFR <60) in individuals with eGFR ≥60 at baseline (n=3,694)



Number at risk

Cluster 1 (SAID)	155	127	112	97	80	38
Cluster 2 (SIDD)	758	614	522	423	344	138
Cluster 3 (SIRD)	743	644	559	499	428	153
Cluster 4 (MOD)	808	674	559	450	366	125
Cluster 5 (MARD)	1230	1080	995	897	769	297
	0	1	2	3	4	5

(B) Cumulative incidence of albuminuria (UACR ≥30 mg/g) in individuals with UACR <30 mg/g at baseline (n=3,168).

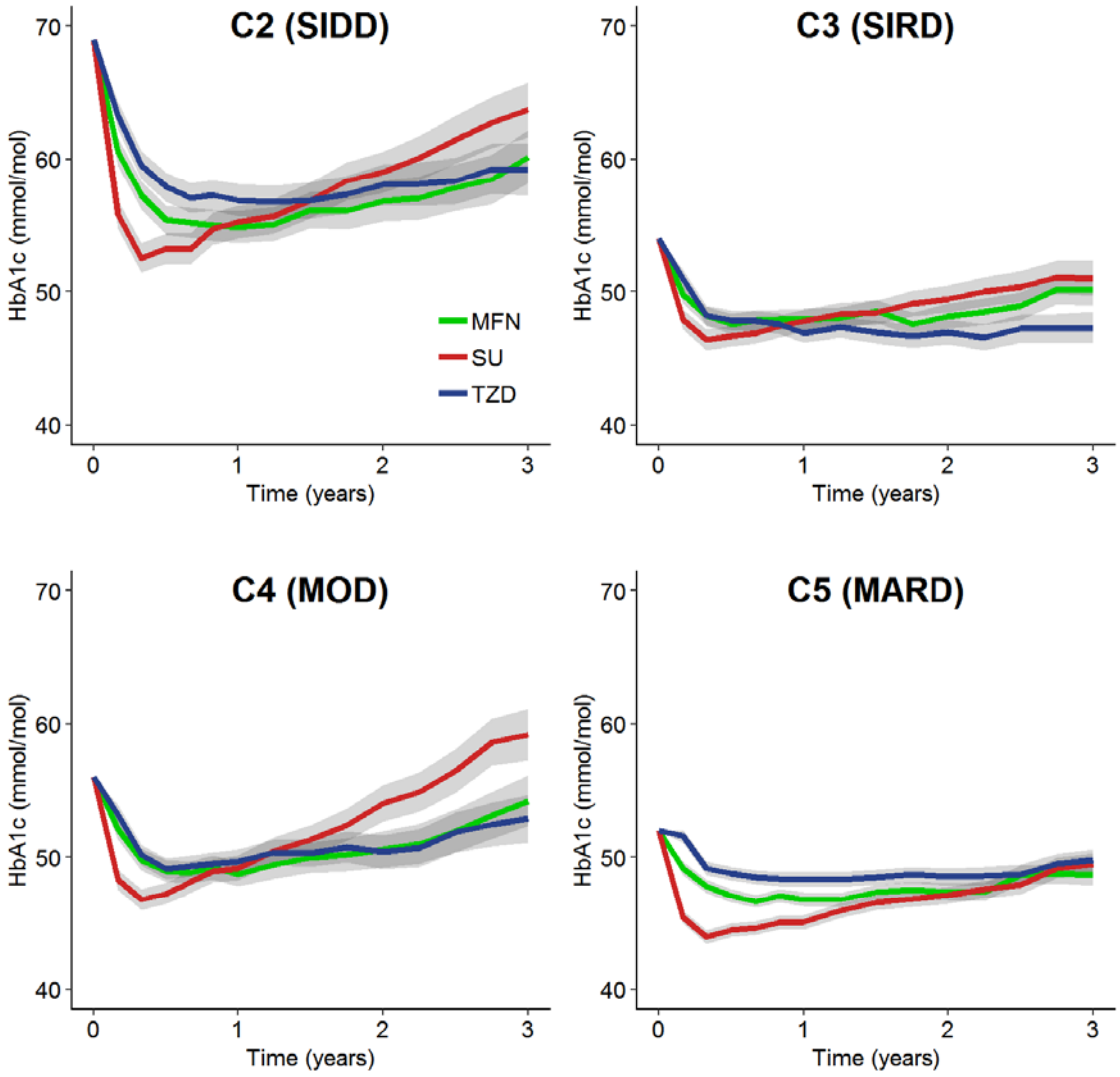


Number at risk

Cluster 1 (SAID)	129	101	91	80	65	27
Cluster 2 (SIDD)	642	499	417	325	241	94
Cluster 3 (SIRD)	637	517	429	364	300	90
Cluster 4 (MOD)	652	520	408	312	232	71
Cluster 5 (MARD)	1108	927	846	727	593	208

Patterns of HbA_{1c} response to the different drugs differed across clusters in ADOPT (Figure 4, Supplementary Figure 8). There was an overall HbA_{1c} benefit with thiazolidinedione therapy in cluster 3 (SIRD), and for sulfonylurea therapy in cluster 5 (MARD) (Table 2). However, the combined clinical features explained more variation in response than the clusters: R^2 was lower for Strategy A) clusters than Strategy B) clinical features (ADOPT R^2 clusters: 0.15 for metformin, 0.20 sulfonylureas, 0.17 thiazolidinediones; R^2 clinical features: 0.35 metformin, 0.33 sulfonylureas, 0.32 thiazolidinediones).

Figure 4: **Change in HbA_{1c} by drug for clusters 2-5 in ADOPT over three years (n=3,607).** Adjusted mean HbA_{1c} over three years by drug. Grey shading shows 95% CIs. For cluster 1 (n=158) see Supplementary Figure 8.

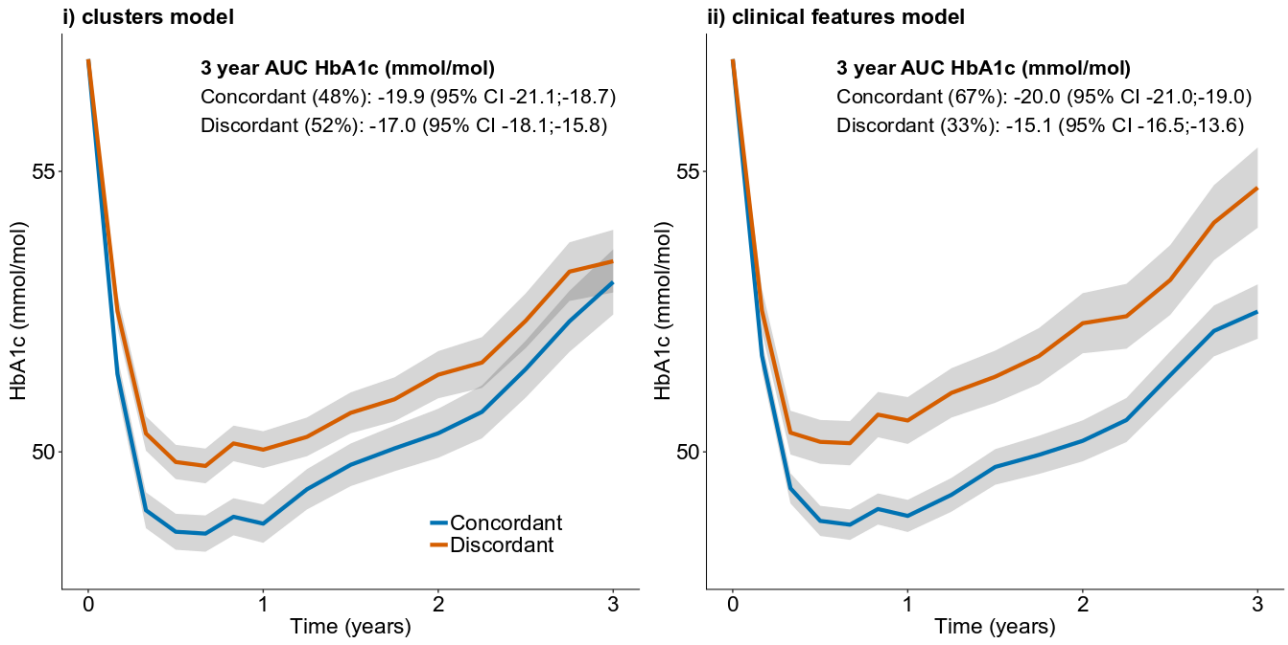


In the independent trial (RECORD) we found clinical features outperformed the clusters for treatment selection. In RECORD we tested the performance for treatment selection of the two strategies developed in ADOPT (Strategy A: selecting therapy based on predicted response to each drug at cluster level; Strategy B selecting therapy based on predicted response to each drug at the individual level based on precise clinical features (see Supplementary Table 9 for ADOPT model coefficients for the clinical features)). Each individual in each trial was assigned as concordant or discordant with the treatment selection rule under Strategy A) clusters and Strategy B) clinical features (Table 2, Supplementary Tables 10-13).

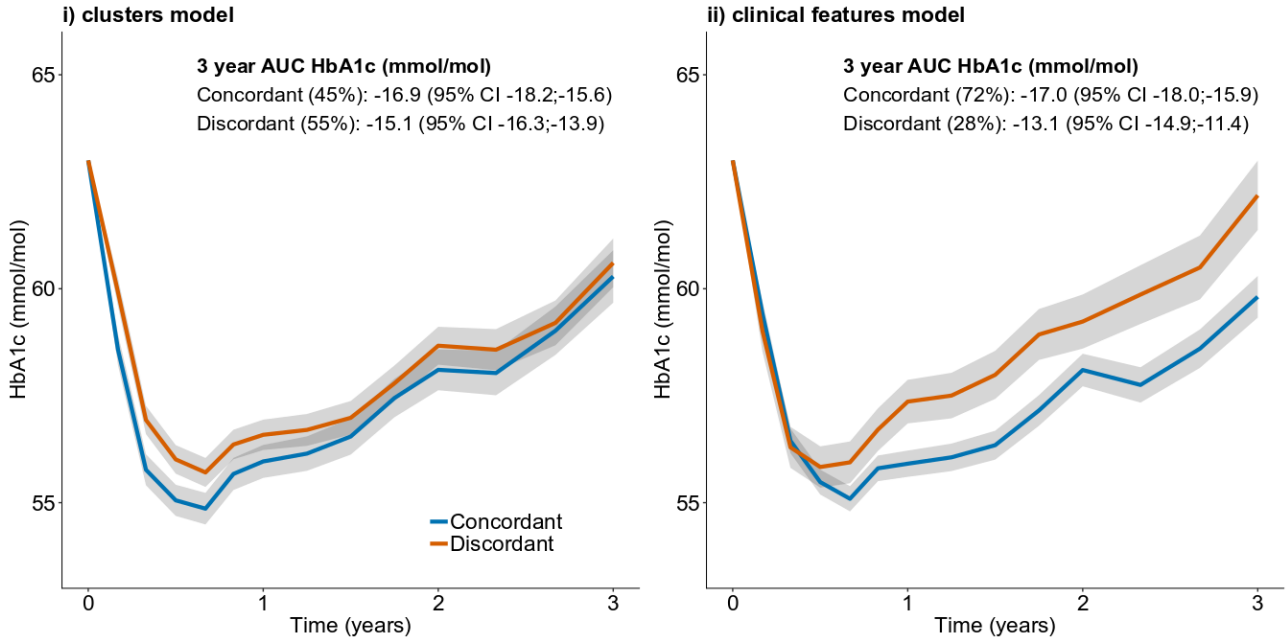
In ADOPT, with both Strategy A) Clusters and Strategy B) clinical features, there was a greater overall HbA_{1c} reduction in the concordant group compared with the discordant group (Figure 5A). In RECORD (validation dataset) there was a greater benefit in the concordant group with Strategy B) clinical features (Figure 5B) than Strategy A) clusters. Strategy B) clinical features outperformed the clusters at all HbA_{1c} thresholds assessed to define concordant and discordant groups in RECORD (Supplementary Table 14).

Figure 5: **Change in HbA_{1c} over three years in concordant and discordant treatment selection groups for i) clusters model and ii) clinical features model**

(A) ADOPT development cohort (n=3,785)



(B) RECORD validation cohort (n=4,057)



There was no evidence of differences between clusters in the risk of cardiovascular hospitalisation or death in RECORD after adjustment for age (Supplementary Figure 9, Supplementary Table 15).

Clusters assigned in ADOPT using the ANDIS cluster centre coordinates were broadly similar to those defined de-novo in ADOPT (Figure 1, Supplementary Figure 10). 58% of individuals were assigned to the same cluster using both the ANDIS derived clusters and de-novo ADOPT clusters (Supplementary Table 16). Differences in outcomes by ANDIS-assigned cluster are shown in the Supplementary Figures 11-13. ADOPT clusters outperformed the ANDIS clusters for treatment response; model performance measures were similar for glycaemic and renal progression (Supplementary Table 17).

Discussion

We found the data-driven clusters of Ahlqvist and colleagues were reproducible in trial data. Clusters differed in glycaemic and renal progression but simple clinical factors features (respectively, age at diagnosis and baseline renal function) performed as well or better to predict progression. To our knowledge, for the first time we show differences by cluster in treatment response. However, clusters were markedly outperformed by models using simple clinical features for both the prediction of glucose-lowering response and for treatment selection. Overall the results suggest there will be greater clinical utility from modelling clinical features directly, rather than from using clinical features to place individuals into subgroups (Figure 6).

Even though there were restricted entry criteria for both the ADOPT and RECORD trials, cluster analysis defined subgroups were very similar to those seen in non-selective Scandinavian cohorts, and subsequently Chinese and US cohorts.(4, 20) This suggests that if the cluster analysis is repeated in the specified way in new datasets it will routinely produce similar clusters.

A key strength of trial data over previous observational data is the availability of protocol driven follow-up, meaning we were able to conduct a systematic assessment and demonstrate the clusters do differ in disease progression. This is a considerable advantage over the previously described routine follow-up where therapy introduction is not protocol driven.(4) Independently of therapy, clusters 1 (SAID), 2 (SIDD) and 4 (MOD) had an increased rate of glycaemic progression.

Differences in the development of renal failure had previously been shown in observational follow-up, and we replicated a faster progression of renal disease in clusters 3 (SIRD) and 5 (MARD), although there was no evidence of a difference in renal progression after accounting for baseline renal function.

We were able to establish that the clusters differ in response to different glucose-lowering therapies. This was possible due to the randomised, systematic therapy given. We found a particular benefit for cluster 3 (SIRD) with thiazolidinediones, and for cluster 5 (MARD) with sulfonylureas.

The fact that clusters are reproducible and can help predict progression and response to therapy is important. However a key question raised in response to the original article is whether it is more clinically useful to use clinical features to assign an individual to a subgroup and then treat in a way that is best for that subgroup, or to use clinical features to predict patient outcomes directly using outcome-specific models.(7) We found simple clinical features were similar or better than the clusters to stratify disease progression and to personalise therapy. A simple model incorporating just age at diagnosis was able to predict glycaemic progression as well as the clusters, having been identified as a key predictor of progression in recent observational analysis.(21) Similarly, baseline renal function explained differences between the clusters in risk of renal progression.

For treatment response we found that models combining four simple clinical measures (age, sex, baseline HbA_{1c} and BMI) explained more variation in response than the clusters. However, this gives little insight into which of the two approaches

is more useful to select between treatment options for an individual patient.(17, 18) A more useful test in this context is to compare the population-level effect on glycaemic response of applying each approach to select treatment.(18) We were able to directly assess this, by comparing the two approaches developed in ADOPT in an independent trial dataset (RECORD). This was possible as some participants in RECORD were randomised to the drug estimated to be 'best' for them using the ADOPT models (concordant group) whilst the remainder were randomised to a not 'best' drug (discordant group). The difference in HbA_{1c} between the two groups provided a measure of the population-level effect of each treatment selection strategy. In RECORD we found a small benefit (1.8 mmol/mol over three years) of selecting therapy by cluster; in contrast there was a greater benefit (3.9 mmol/mol) selecting treatment using the clinical features model. These results suggest that attempts to personalise treatment in type 2 diabetes will have most clinical utility if based on the use of continuous phenotypic measures, rather than subgroup assignment.

Strengths of this study include the use of data from two large, long-term, randomised trials, in which we were able to not only reproduce the clustering approach of Ahlqvist and colleagues, but to describe diabetes progression and treatment response in protocol-driven follow-up. Furthermore we were able to test treatment selection based on clusters compared to clinical features in an independent validation dataset. The treatment selection rule we applied was designed to test clinical utility in this study, rather than to maximise outcomes for the population or individuals. Approaches to evaluate treatment selection strategies are not well-developed and are the subject of on-going methodological research.(17) A limitation

of our study is the potential non-representativeness of participants due to the original trial exclusion criteria. Both ADOPT and RECORD had exclusion criteria based on blood glucose levels and age (and BMI in RECORD); these clinical variables informed the cluster analysis. Despite this we found that the clusters were reproducible, with a pattern of differences in phenotypic measures that closely matched those previously reported. Given the variables informing the cluster analysis are not independent and are likely to be similarly correlated in most people with diabetes, this reproducibility is not surprising,(7) although similarly to the original study we lacked data on non-white ethnicities (ADOPT was 88% Caucasian, RECORD 99%). Due to the design of the trials we were unable to evaluate some outcomes explored in the original study such as time to insulin, and we lacked power to evaluate other outcomes including development of end-stage renal disease. A further limitation was the therapy used in the trials; evaluation of heterogeneity in treatment response for the newer drug classes DPP4 inhibitors, SGLT2 inhibitors and GLP-receptor agonists would be of considerable interest.

An important difference between this study and the original study by Ahlqvist and colleagues was in the analysis of renal progression. Whilst we excluded individuals with pre-existing kidney disease, in the Scandinavian population-based cohorts people with pre-existing kidney disease when diagnosed with diabetes were not excluded and the onset of renal dysfunction was set to the first time that an abnormal value was found on clinical testing post diabetes diagnosis.

Precision medicine is successfully established in monogenic and neonatal diabetes, where it has been possible to define discrete etiological subtypes with differing genetic causes that have very different optimal treatment requirements.(22-24) A key

difference from type 2 diabetes is that in these cases the subgroups have discrete and non-overlapping aetiologies and can be robustly defined by genetic sequencing. In contrast, the study of Ahlqvist and colleagues and other recent attempts to characterise the heterogeneity in type 2 diabetes have identified clusters with limited clinical utility as they are non-aetiological, overlapping, highly dependent on the variables used to classify them and cannot be robustly defined at an individual level.(4, 25) Even genetic susceptibility clusters, which do have the advantage of being fixed throughout life, have not led to the identification of discrete etiological diabetes subtypes, although they offer insight into mechanistic pathways underlying heterogeneity.(26)

The known heterogeneity in type 2 diabetes, together with the differences we have observed in clinical outcomes, raises the possibility of a practical clinical application of precision medicine in type 2 diabetes in the near future. Our study supports the suggestion that the optimal approach to tailor management based on risk of progression and therapeutic response will be to use ‘precise’ continuous phenotypic measures to predict specific outcomes for individuals using multivariable models, rather than define subgroups and assume all individuals are homogenous within each subgroup.(7) In particular, individual clinical characteristics have been shown to have robust associations with response to specific type 2 diabetes drug options.(6, 27-29) These studies raise the possibility that the relative glucose-lowering benefit of the different drugs might be identifiable by combining simple clinical measures in a model for treatment selection. This will require systematic assessment of associations between other patient features (including lifestyle factors, biomarkers and concomitant medications) beyond those assessed in this study. The advantage

of such an approach is that the clinical features used are already part of routine clinical care. Similarly, further systematic assessment of associations between clinical patient features and glycaemic and renal progression will be required to determine whether individuals at high or low risk of progression can be robustly identified.

The methodology we have applied in this study, harnessing existing individual-level trial data to test a precision medicine strategy developed in other data, offers an exciting, low-cost framework to evaluate novel precision medicine approaches without a prospective trial. Such trial datasets are increasingly available to researchers to answer secondary research questions.(30) The approach we used of a direct comparison of different approaches in an independent data set is a good model for defining their relative performance. When defining utility of models in future studies it will be important to interrogate multiple relevant outcomes as well as glycaemia, including cardiovascular outcomes, microvascular complications, and non-glycaemic effects of specific drugs including weight change and side-effects

In conclusion, we have shown cluster-defined subgroups are reproducible and can help to define individuals that differ in the risk of diabetes progression and in glycaemic response to common therapeutic options. Our study demonstrates a ‘prediction model’ approach combining phenotypic measures to predict specific outcomes for individual patients is likely to have greater clinical utility than subgroup assignment. Existing trial data offer an exciting opportunity to evaluate the potential of precision medicine approaches to improve clinical outcomes in type 2 diabetes.

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Supplementary Material

Cluster assignment and characteristics (ADOPT and RECORD)

Supplementary Table 1: ADOPT cluster distributions, overall and by sex (n=4,003). SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MOD=mild obesity-related diabetes. MARD=mild age-related diabetes.

	Male		Female		Overall	
Cluster	**N**	**%**	**N**	**%**	**N**	**%**
1 SAID	94	4%	74	4%	168	4%
2 SIDD	506	22%	302	18%	808	20%
3 SIRD	448	19%	369	22%	817	20%
4 MOD	411	18%	447	26%	858	21%
5 MARD	844	37%	508	30%	1352	34%

Supplementary Table 2: Cluster centre coordinates in ADOPT

	Cluster	HbA1c	BMI	Age at diagnosis	HOMA2-B	HOMA2-IR
Females	C2 (SIDD)	1.357582	-0.438702	0.209430	-0.873420	-0.508708
	C3 (SIRD)	-0.207560	0.801772	-0.048181	1.168571	1.276217
	C4 (MOD)	-0.283972	0.282755	-0.956176	-0.257172	-0.274304
	C5 (MARD)	-0.406427	-0.570389	0.751853	-0.103295	-0.383230
Males	C2 SIDD)	1.146754	-0.334983	-0.300259	-0.780702	-0.448964
	C3 (SIRD)	-0.419911	0.021167	0.587122	1.132740	0.960985
	C4 (MOD)	0.102709	1.357982	-0.838457	0.480047	0.743829
	C5 (MARD)	-0.514633	-0.471697	0.276666	-0.366980	-0.603150

Supplementary Table 3: ADOPT Cluster characteristics by sex (n=4,003). SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MOD=mild obesity-related diabetes. MARD=mild age-related diabetes. HOMA2-B=homoeostatic model assessment 2 estimates of β-cell function. HOMA2-IR=homoeostatic model assessment 2 estimates of insulin resistance.

A) Females

	Number of participants (%)	HbA1c (mmol/mol)		BMI kg/m2		Age at diagnosis (years)		HOMA2-B (%)		HOMA2-IR (%)	
Cluster		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
1 SAID	74 (4%)	59	50-65	33	28-38	59	51-64	63	46-87	2.4	1.5-3.4
2 SIDD	302 (18%)	69	65-75	30	27-34	57	52-64	49	38-59	2.2	1.7-2.8
3 SIRD	369 (22%)	55	49-61	39	35-43	55	49-62	102	87-125	4.3	3.8-5.0
4 MOD	447 (26%)	54	50-58	35	31-40	46	41-50	67	54-79	2.6	2.1-3.1
5 MARD	508 (30%)	53	49-57	30	27-33	64	58-68	70	58-83	2.5	1.9-3.0

B) Males

	Number of participants (%)	HbA1c (mmol/mol)		BMI kg/m2		Age at diagnosis (years)		HOMA2-B (%)		HOMA2-IR (%)	
Cluster		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
1 SAID	94 (4%)	57	53-64	29	27-33	57	49-64	60	46-77	2.4	1.7-3.1
2 SIDD	506 (22%)	67	63-73	29	27-32	53	46-60	49	38-59	2.3	1.8-2.8
3 SIRD	448 (19%)	52	48-57	31	29-34	63	57-68	100	86-117	3.7	3.2-4.6
4 MOD	411 (18%)	57	52-63	37	34-42	49	41-54	83	68-98	3.5	3.0-4.3
5 MARD	844 (37%)	52	48-56	28	26-31	59	53-65	60	51-72	2.2	1.7-2.6

Supplementary Table 4: Cluster characteristics for each trial population

ADOPT (n=4,003). Median (interquartile range) unless stated.

	1 SAID	2 SIDD	3 SIRD	4 MOD	5 MARD
N. participants (%)	168 (4%)	808 (20%)	817 (20%)	858 (21%)	1352 (34%)
HbA1c (mmol/mol)	58 (52-64)	67 (64-74)	53 (48-60)	55 (51-61)	53 (49-56)
BMI (kg/m²)	30 (27-36)	29 (27-32)	34 (30-38)	36 (33-40)	29 (26-31)
Age at diagnosis (years)	57 (49-64)	55 (48-61)	59 (53-66)	47 (41-52)	61 (55-66)
HOMA2-B (%)*	61 (46-83)	49 (38-59)	101 (87-121)	74 (59-89)	64 (53-76)
HOMA2-IR*	2.4 (1.6-3.3)	2.3 (1.8-2.8)	4.0 (3.4-4.7)	3.1 (2.4-3.7)	2.3 (1.8-2.7)
Male sex (%)	94 (56%)	506 (63%)	448 (55%)	411 (48%)	844 (62%)
Ethnicity (% White)	158 (94%)	745 (92%)	804 (98%)	801 (93%)	1327 (98%)
Fasting glucose (mmol/l)	8.3 (7.6-9.3)	9.2 (8.4-10.2)	7.9 (7.2-8.7)	8.3 (7.5-9.2)	8.0 (7.4-8.6)
Fasting insulin (pmol/L)	108 (70-150)	93 (72-129)	208 (150-280)	158 (114-215)	96 (72-126)
Fasting C-peptide (nmol/L)	0.9 (0.6-1.3)	0.8 (0.7-1.0)	1.6 (1.4-1.8)	1.2 (1.0-1.4)	0.9 (0.7-1.1)
eGFR (ml/min per 1.73m²)**	93 (82-103)	98 (87-106)	90 (77-100)	104 (96-112)	93 (82-100)
eGFR <60 at baseline (%)**	4 (2%)	14 (2%)	41 (5%)	8 (1%)	44 (3%)
Albuminuria (mg/g)***	7 (4-16)	8 (4-17)	8 (4-18)	7 (4-19)	6 (4-13)
Albuminuria ≥ 30 at baseline (%)***	26 (16%)	126 (16%)	145 (18%)	154 (18%)	158 (12%)
HDL (mmol/L)	1.2 (1.1-1.5)	1.2 (1.0-1.5)	1.1 (1.0-1.3)	1.1 (1.0-1.4)	1.3 (1.1-1.5)
LDL (mmol/L)	3.0 (2.4-3.6)	3.3 (2.7-4.0	2.9 (2.4-3.6)	3.1 (2.5-3.7)	3.2 (2.6-3.8)
ALT (U/L)	21 (16-31)	22 (17-31)	26 (19-36)	26 (18-37)	21 (16-29)

*Calculated with HOMA2 calculator using fasting glucose and fasting C-peptide
** Calculated with CKD-EPI formula ***71 individuals with missing albuminuria at baseline

RECORD (n=4,148; ADOPT-defined clusters). Median (interquartile range) unless stated.

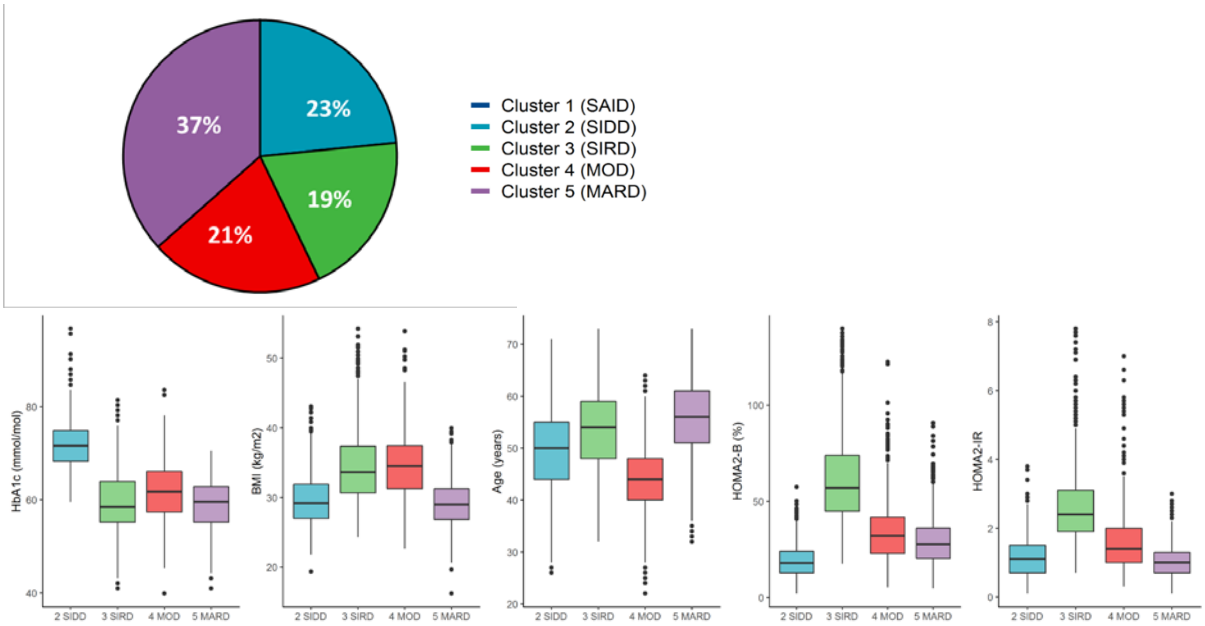
	1 SAID	2 SIDD	3 SIRD	4 MOD	5 MARD
N. participants (%)	NA	974 (23%)	803 (19%)	852 (21%)	1519 (37%)
HbA1c (mmol/mol)		72 (68-75)	58 (55-64)	62 (57-66)	60 (55-63)
BMI (kg/m²)		29 (27-32)	34 (31-37)	35 (31-37)	29 (27-31)
Age at diagnosis (years)		50 (44-55)	54 (48-59)	44 (40-48)	56 (51-61)
HOMA2-B (%)*		18 (13-24)	57 (45-74)	32 (23-42)	28 (20-36)
HOMA2-IR*		1.1 (0.7-1.5)	2.4 (1.9-3.1)	1.4 (1.0-2.0)	1.0 (0.7-1.3)
Diabetes duration (years)		7 (4-11)	5 (3-7)	6 (4-10)	5 (3-8)
Male sex (%)		571 (59%)	361 (45%)	313 (37%)	898 (59%)
Ethnicity (% White)		964 (99%)	795 (99%)	841 (99%)	1510 (99%)
Fasting glucose (mmol/l)		11 (10-13)	9 (8-10)	10 (8-11)	9 (8-10)
Fasting insulin (pmol/L)		48 (32-66)	114 (91-146)	67 (48-91)	45 (32-61)
Fasting C-peptide (nmol/L)		NA	NA	NA	NA
eGFR (ml/min per 1.73m²)**		100 (91-106)	97 (88-105)	106 (99-112)	96 (87-102)
eGFR <60 at baseline (%)**		13 (1%)	28 (3%)	9 (1%)	30 (2%)
Albuminuria (mg/g)***		9 (5-25)	9 (5-23)	9 (5-24)	8 (4-17)
Albuminuria ≥ 30 at baseline (%)***		190 (22%)	142 (20%)	149 (20%)	209 (16%)
HDL (mmol/L)		1.2 (1.0-1.4)	1.1 (0.9-1.3)	1.2 (1.0-1.4)	1.2 (1.0-1.4)
LDL (mmol/L)		3.4 (2.8-4.0)	3.2 (2.5-3.8)	3.2 (2.6-3.8)	3.3 (2.6-3.8)
ALT (U/L)		25 (19-36)	29 (21-41)	26 (19-39)	23 (17-31)

*Calculated with HOMA2 calculator using fasting glucose and fasting insulin as fasting C-peptide not available
** Calculated with CKD-EPI formula, 2 individuals missing eGFR at baseline ***479 individuals with missing albuminuria at baseline

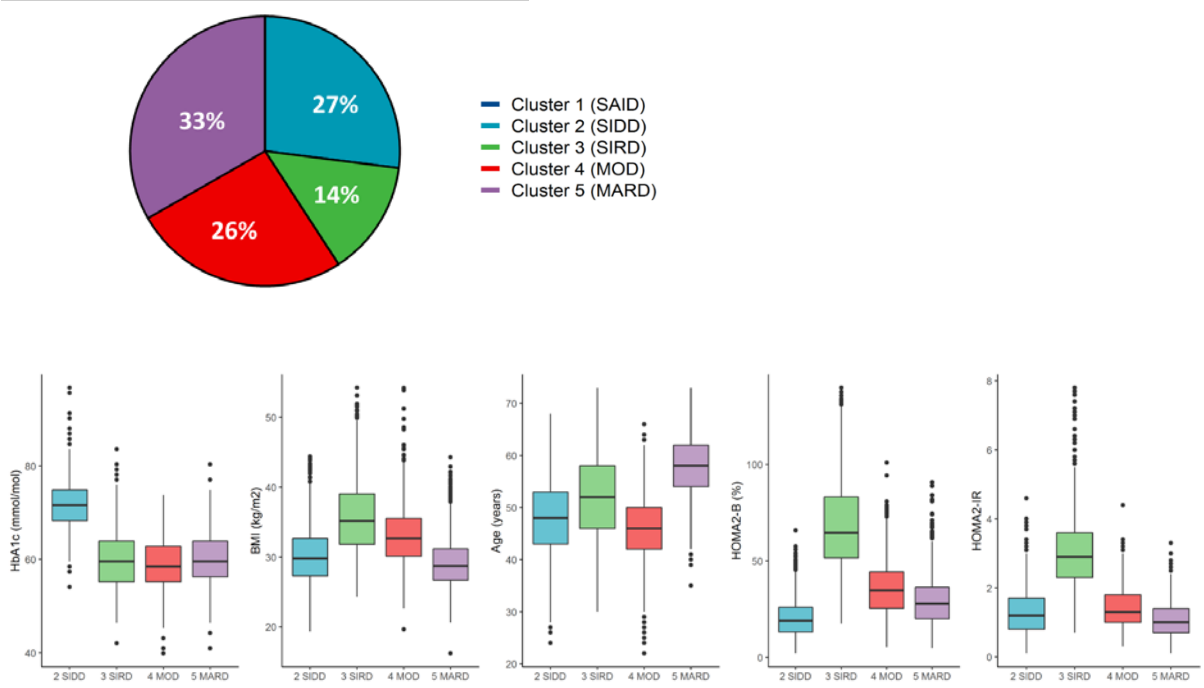
Supplementary Figure 1: clusters characteristics in RECORD. Cluster distribution and cluster characteristics (n=4,148). RECORD participants assignment and distributions of baseline clinical characteristics according to k-means clustering (A) Clusters derived in ADOPT and assigned to RECORD participants (B) Clusters derived in RECORD and assigned to RECORD participants.

SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MOD=mild obesity-related diabetes. MARD=mild age-related diabetes. HOMA2-B=homoeostatic model assessment 2 estimates of β-cell function. HOMA2-IR=homoeostatic model assessment 2 estimates of insulin resistance.

(A) ADOPT derived clusters

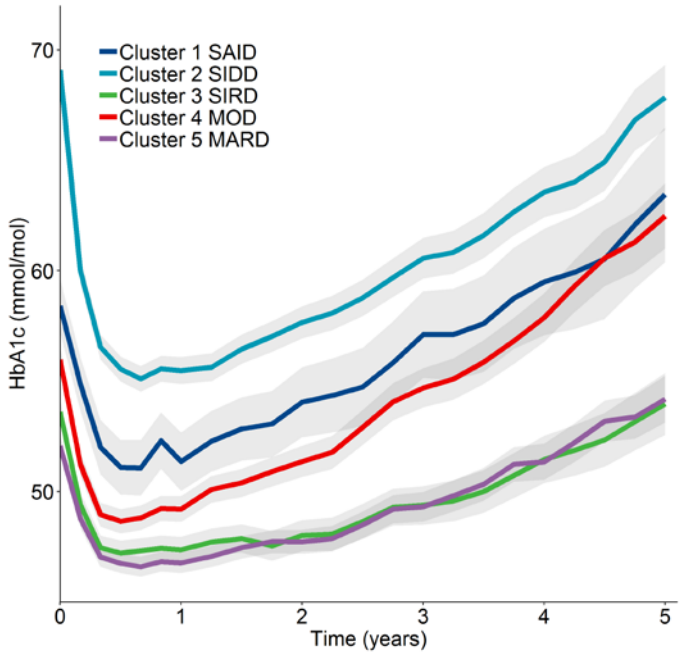


(B) RECORD derived clusters



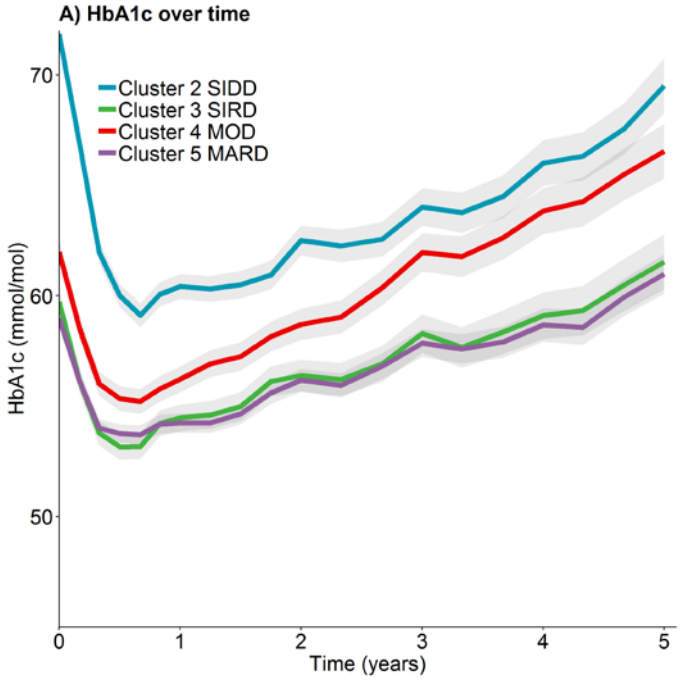
Glycaemic progression

Supplementary Figure 2: HbA1c over time from randomisation by cluster in ADOPT (n=3,802).



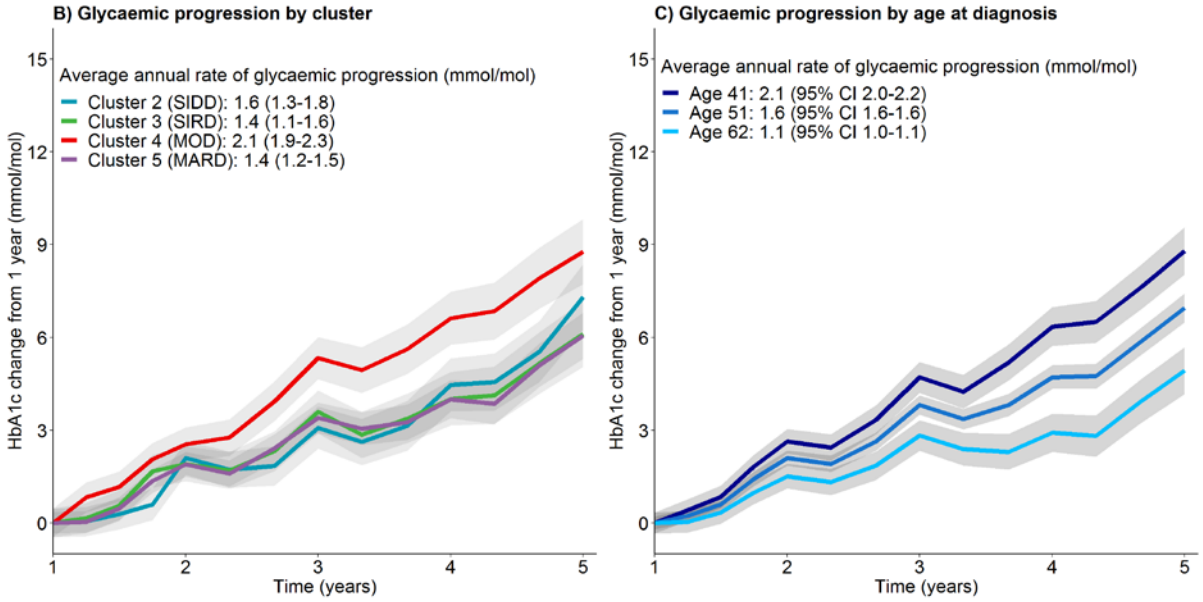
Supplementary Figure 3: HbA1c in RECORD

(A) HbA1c over time from randomisation by cluster (n=4,057);



Supplementary Figure 3 (cont.): HbA1c in RECORD.

(B) Glycaemic progression from 1 year by ADOPT derived cluster (n=3,586); (C) Glycaemic progression from 1 year by age at diagnosis (10th, 50th and 90% percentile of RECORD participants) (n=3,586). Data are estimates from repeated measures mixed effects models.



Supplementary Table 5: Glycaemic progression model performance measures to compare model using clusters and model using age at diagnosis. A higher adequacy index suggests a better model (calculated as model LR x^2 / Combined model LR x^2)

A) ADOPT

	R^2	AIC	LR x^2	Adequacy Index
Clusters	0.084	221404	1225	0.95
Age at diagnosis	0.088	221318	1210	0.94
Combined model (clusters + age at diagnosis)	0.093	221371	1292	1.00

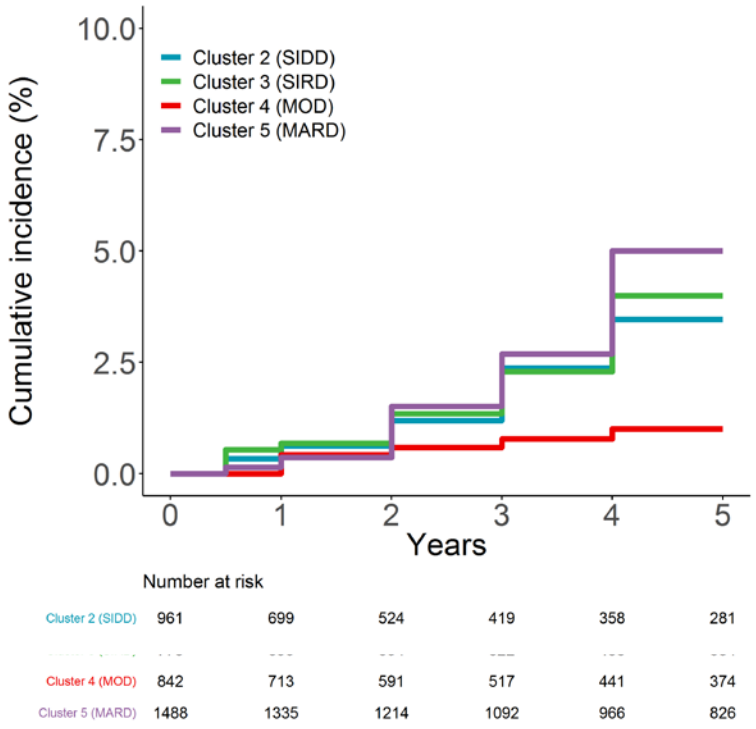
B) RECORD

	R^2	AIC	LR x^2	Adequacy Index
Clusters	0.048	274658	1065	0.89
Age at diagnosis	0.052	274624	1099	0.92
Combined model (clusters + age at diagnosis)	0.055	274642	1196	1.00

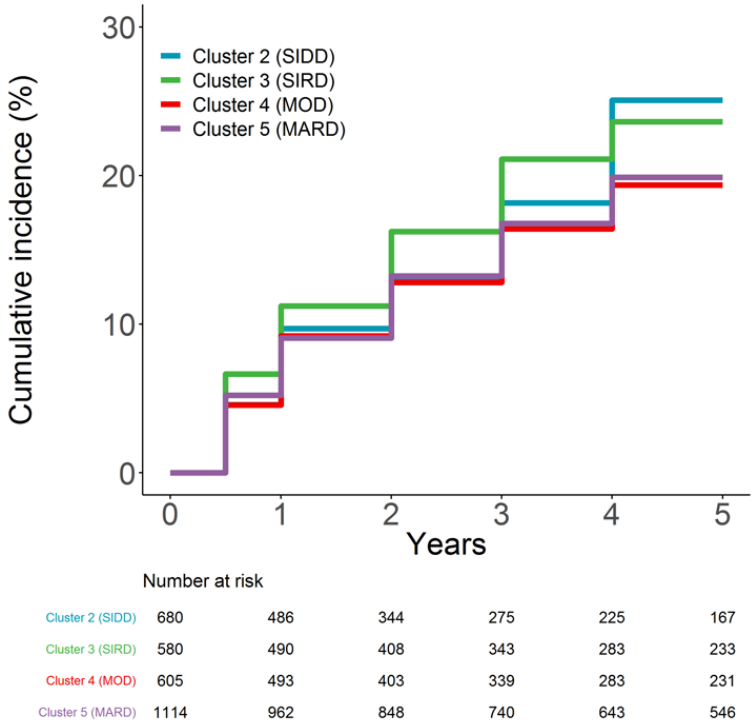
Renal progression

Supplementary Figure 4: Renal progression by cluster in RECORD (clusters derived from ADOPT)

(A) Cumulative incidence of CKD Stage 3 (confirmed eGFR <60) in individuals with eGFR ≥60 at baseline (n=4,066). eGFR calculated using CKD-EPI formula.



(B) Cumulative incidence of albuminuria (UACR ≥30 mg/g) in individuals with UACR <30 mg/g at baseline (n=2,979).



Supplementary Table 6: Risk of renal progression by cluster in RECORD (clusters derived from ADOPT)

(A) Time to CKD Stage 3 (n=4,066). eGFR calculated using CKD-EPI formula.

	No.	Person years at risk	Events	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Time to CKD					
Cluster					
C1 (SAID)	NA	NA	NA	NA	NA
C2 (SIDD)	961	2551	17	1.00 (ref)	1.00 (ref)
C3 (SIRD)	775	2789	22	1.12 (0.60-2.11)	0.96 (0.51-1.81)
C4 (MOD)	842	2811	6	0.31 (0.12-0.78)	0.57 (0.22-1.45)
C5 (MARD)	1488	5658	55	1.37 (0.79-2.36)	1.16 (0.67-2.00)

*Adjusted for baseline eGFR

(B) Time to albuminuria (n=2,979)

	No.	Person years at risk	Events	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Time to albuminuria					
Cluster					
C1 (SAID)	NA	NA	NA	NA	NA
C2 (SIDD)	680	1679	103	1.00 (ref)	1.00 (ref)
C3 (SIRD)	580	1860	113	1.04 (0.80-1.36)	1.02 (0.78-1.34)
C4 (MOD)	605	1869	90	0.82 (0.62-1.09)	0.82 (0.62-1.09)
C5 (MARD)	1114	3906	188	0.85 (0.66-1.08)	0.92 (0.72-1.17)

*Adjusted for baseline UACR

Supplementary Table 7: Time to CKD Stage 3. eGFR calculated using MDRD formula.

(A) ADOPT (n=3,650)

	No.	Person years at risk	Events	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Time to CKD					
Cluster					
C1 (SAID)	152	492	7	3.00 (1.16-7.72)	1.67 (0.64-4.32)
C2 (SIDD)	748	2235	11	1.00 (ref)	1.00 (ref)
C3 (SIRD)	729	2427	35	2.99 (1.53-5.92)	1.65 (0.84-3.26)
C4 (MOD)	799	2406	11	0.93 (0.40-2.14)	1.33 (0.57-3.06)
C5 (MARD)	1222	4325	41	2.00 (1.03-3.90)	1.52 (0.78-2.97)

*Adjusted for baseline eGFR

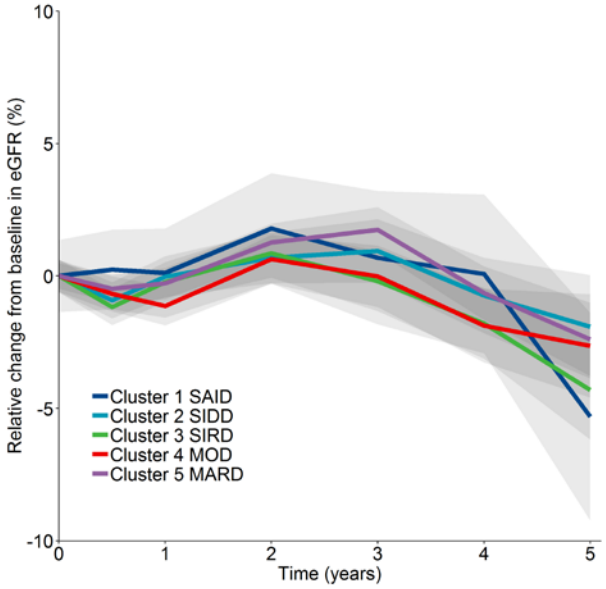
(B) RECORD (n=4,032)

	No.	Person years at risk	Events	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Time to albuminuria					
Cluster					
C1 (SAID)	NA	NA	NA	NA	NA
C2 (SIDD)	956	2528	20	1.00 (ref)	1.00 (ref)
C3 (SIRD)	769	2753	30	1.31 (0.74-2.31)	1.10 (0.91-1.94)
C4 (MOD)	838	2781	15	0.66 (0.34-1.28)	0.98 (0.50-1.91)
C5 (MARD)	1469	5570	74	1.58 (0.96-2.59)	1.41 (0.86-2.32)

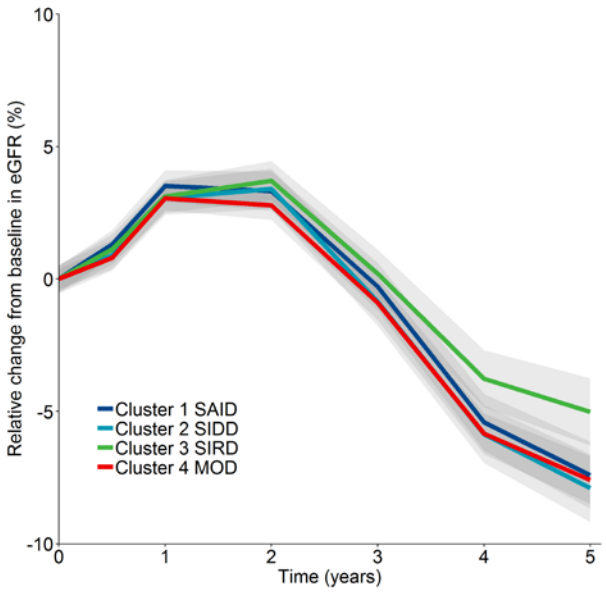
*Adjusted for baseline eGFR

Supplementary Figure 5: Relative change in eGFR from baseline, by cluster. eGFR calculated using CKD-EPI formula. Estimates are from mixed effects models.

A) ADOPT (n=3,694)

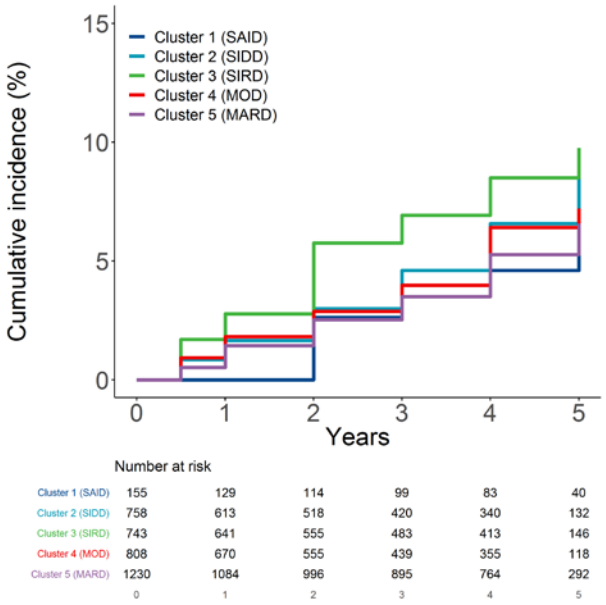


B) RECORD (n=4,066)



Supplementary Figure 6: Cumulative incidence of 30% relative change in eGFR from baseline, by cluster. eGFR calculated using CKD-EPI formula.

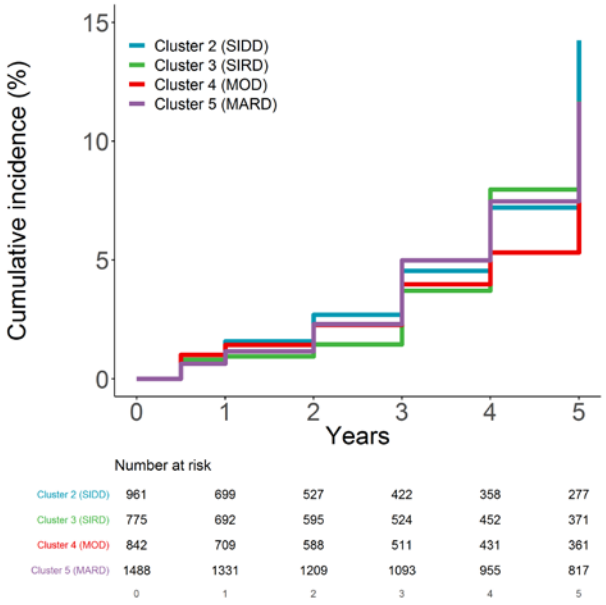
A) ADOPT (n=3,694)



Number at risk

	0	1	2	3	4	5
Cluster 1 (SAID)	155	129	114	99	83	40
Cluster 2 (SIDD)	758	613	518	420	340	132
Cluster 3 (SIRD)	743	641	555	483	413	146
Cluster 4 (MOD)	808	670	555	439	355	118
Cluster 5 (MARD)	1230	1084	996	895	764	292

B) RECORD (n=4,066)



Number at risk

	0	1	2	3	4	5
Cluster 2 (SIDD)	961	699	527	422	358	277
Cluster 3 (SIRD)	775	692	595	524	452	371
Cluster 4 (MOD)	842	709	588	511	431	361
Cluster 5 (MARD)	1488	1331	1209	1093	955	817

Supplementary Table 8: Risk of 30% relative change in eGFR from baseline by cluster. eGFR calculated using CKD-EPI formula.

(A) ADOPT (n=3,694)

	No.	Person years at risk	Events	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Time to 30% relative change in eGFR					
Cluster					
C1 (SAID)	155	508	7	0.88 (0.39-1.97)	0.78 (0.35-1.77)
C2 (SIDD)	758	2239	35	1.00 (ref)	1.00 (ref)
C3 (SIRD)	743	2452	51	1.33 (0.87-2.05)	1.16 (0.75-1.79)
C4 (MOD)	808	2387	34	0.92 (0.57-1.48)	1.05 (0.65-1.69)
C5 (MARD)	1230	4359	54	0.79 (0.51-1.20)	0.72 (0.47-1.10)

*Adjusted for baseline eGFR

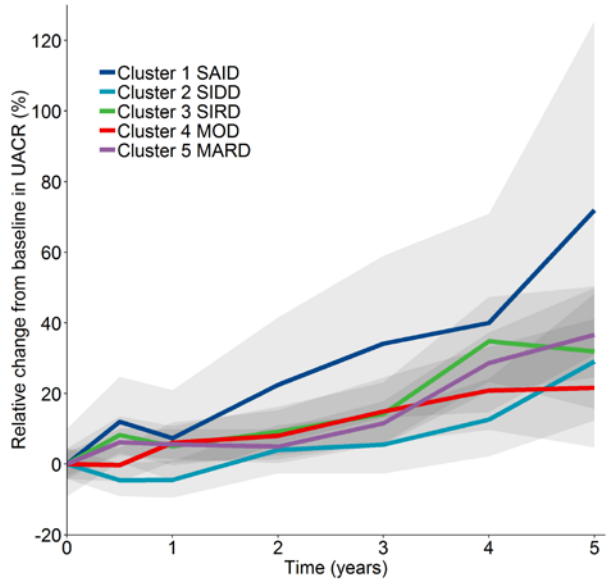
(B) RECORD (n=4,066)

	No.	Person years at risk	Events	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Time to 30% relative change in eGFR					
Cluster					
C1 (SAID)	NA	NA	NA	NA	NA
C2 (SIDD)	961	2547	58	1.00 (ref)	1.00 (ref)
C3 (SIRD)	775	2771	57	0.83 (0.58-1.20)	0.78 (0.54-1.12)
C4 (MOD)	842	2773	40	0.59 (0.39-0.88)	0.74 (0.49-1.11)
C5 (MARD)	1488	5625	122	0.85 (0.62-1.16)	0.78 (0.57-1.07)

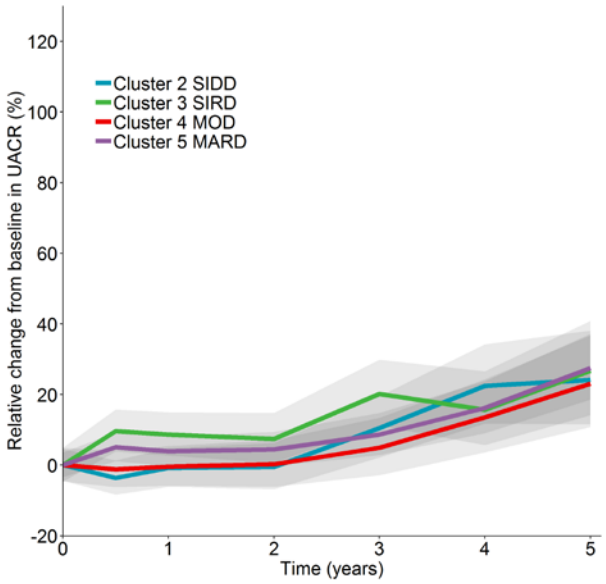
*Adjusted for baseline eGFR

Supplementary Figure 7: Relative change in urinary albumin to creatinine ratio from baseline, by cluster. Estimates are from mixed effects models with UACR modelled on log scale.

A) ADOPT (n=3,168)

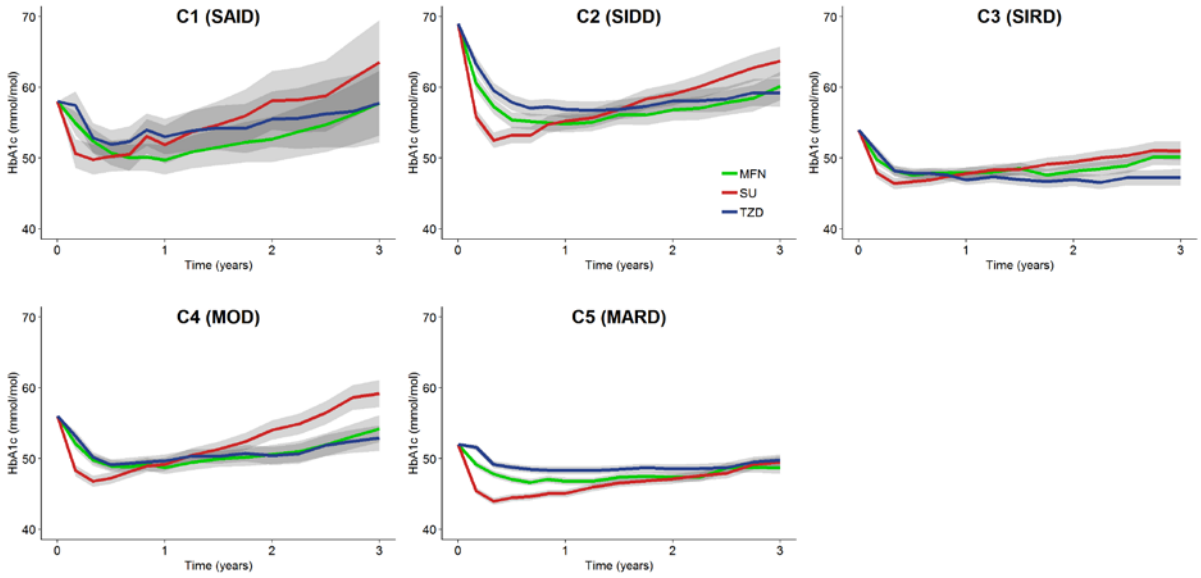


B) RECORD (n=2,979)



HbA1c response

Supplementary Figure 8: Changes in HbA1c (ADOPT trial, n=3,785). Adjusted mean HbA1c over 3 years by drug for clusters 1-5 (repeated measures mixed model). Grey shading shows 95% CIs.



Supplementary Table 9: Beta coefficients from mixed effects models for clinical features, by drug. For continuous features beta coefficients represent the change in HbA1c response for a 1-unit increase in the clinical feature. A negative coefficient indicates a higher value of the clinical feature is associated with greater reduction in HbA1c.

	Metformin	Sulfonylureas	Thiazolidinediones
Baseline HbA1c (time 0)*	0.69 (0.66;0.72)	0.59 (0.55;0.63)	0.69 (0.65;0.73)
BMI	-0.02 (-0.07;0.03)	0.03 (-0.02;0.09)	-0.11 (-0.16;-0.06)
Age at diagnosis	0.00 (-0.03;0.03)	-0.02 (-0.05;0.01)	-0.02 (-0.06;0.01)
Sex: Male	0.53 (-0.07;1.13)	-1.54 (-2.19;-0.89)	0.59 (-0.06;1.23)

*Full baseline HbA1c:study visit interaction terms not reported for brevity.

Treatment selection

Supplementary Table 10

ADOPT number of concordant individuals, by cluster, for treatment selection at 3 years based on Strategy A) treatment selection based on clusters

	Discordant	Concordant
Cluster		
C1 (SAID)	93	65
C2 (SIDD)	257	502
C3 (SIRD)	510	265
C4 (MOD)	272	539
C5 (MARD)	838	424

Supplementary Table 11

ADOPT number (%) of concordant individuals, by drug at 3 years, for

Strategy A) treatment selection based on clusters

	Discordant	Concordant
Overall	1970 (52%)	1795 (48%)
By randomised drug:		
Metformin	702 (55%)	569 (45%)
Sulfonylureas	555 (45%)	672 (55%)
Thiazolidinedione	713 (56%)	554 (44%)

Strategy B) treatment selection based on clinical features

	Discordant	Concordant
Overall	1227 (33%)	2538 (67%)
By randomised drug:		
Metformin	225 (18%)	1046 (82%)
Sulfonylureas	455 (37%)	772 (63%)
Thiazolidinedione	547 (43%)	720 (57%)

Supplementary Table 12

RECORD number of concordant individuals, by cluster, for treatment selection at 3 years based on Strategy A) treatment selection based on clusters

	Discordant	Concordant
Cluster		
C1 (SAID)	-	-
C2 (SIDD)	455	493
C3 (SIRD)	406	386
C4 (MOD)	239	594
C5 (MARD)	1121	363

Supplementary Table 13

RECORD number (%) of concordant individuals, by drug at 3 years, for a) treatment selection based on clusters

Strategy A) treatment selection based on clusters

	Discordant	Concordant
Overall	2221 (55%)	1836 (45%)
By randomised drug:		
Metformin	540 (54%)	463 (46%)
Sulfonylureas	469 (46%)	546 (54%)
Thiazolidinedione	1212 (59%)	827 (41%)

Strategy B) treatment selection based on clinical features

	Discordant	Concordant
Overall	1117 (28%)	2940 (72%)
By randomised drug:		
Metformin	23 (2%)	980 (98%)
Sulfonylureas	494 (49%)	521 (51%)
Thiazolidinedione	600 (29%)	1439 (71%)

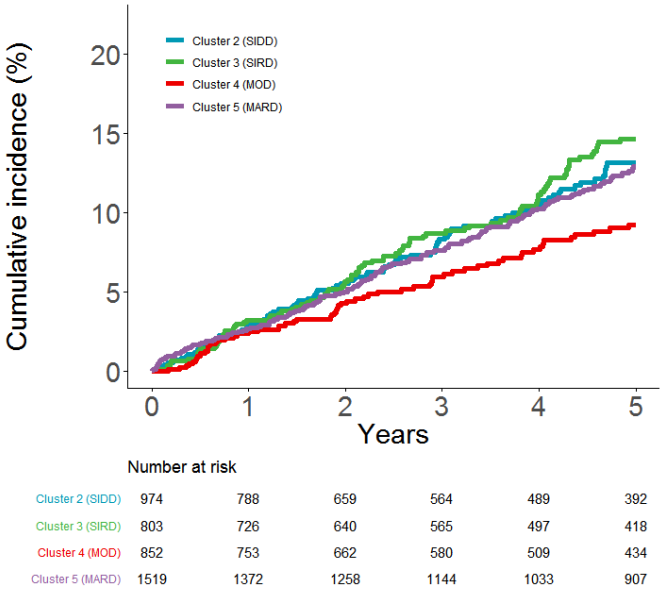
Supplementary Table 14: Cumulative HbA1c reduction at 3 years in concordant and discordant treatment selection groups using different HbA1c thresholds to define concordant/discordant groups, for clusters model and clinical features model (RECORD n=4,057)

HbA1c threshold (mmol/mol	Clusters 3 Year AUC HbA1c		Continuous features 3 Year AUC HbA1c	
	Concordant	Discordant	Concordant	Discordant
0	-18.0 (-19.6;-16.4)	-15.0 (-16.1;-14.0)	-18.3 (-20.0;-16.7)	-14.8 (-15.9;-13.8)
1	-17.0 (-18.4;-15.6)	-15.2 (-16.3;-14.0)	-18.3 (-19.6;-16.9)	-13.9 (-15.1;-12.7)
2	-17.0 (-18.4;-15.6)	-15.2 (-16.3;-14.0)	-17.6 (-18.7; -16.5)	-13.2 (-14.7;-11.8)
3	-16.9 (-18.2;-15.6)	-15.1 (-16.3;-13.9)	-17.0 (-18.0;-15.9)	-13.1 (-14.9;-11.4)
4	-16.9 (-18.1;-15.7)	-14.9 (-16.2;-13.6)	-16.6 (-17.5;-15.6)	-13.4 (-15.4;-11.4)

Cardiovascular outcomes (RECORD trial)

Supplementary Figure 9: Cumulative incidence of cardiovascular hospitalisation or death, by ADOPT-derived cluster.

RECORD (n=4,057)



Supplementary Table 15: Risk of cardiovascular hospitalisation or death by cluster in RECORD (clusters derived from ADOPT)

RECORD (n=4,057)

	No.	Person years at risk	Events	Hazard ratio (95% CI)	
				Unadjusted	Adjusted*
Time to cardiovascular hospitalisation or death					
Cluster					
C1 (SAID)	NA	NA	NA	NA	NA
C2 (SIDD)	948	3172	88	1.00 (ref)	1.00 (ref)
C3 (SIRD)	792	3038	94	1.11 (0.83-1.49)	1.06 (0.79-1.41)
C4 (MOD)	833	3141	62	0.71 (0.51-0.98)	1.02 (0.73-1.43)
C5 (MARD)	1484	5996	161	0.97 (0.74-1.25)	0.79 (0.61-1.03)

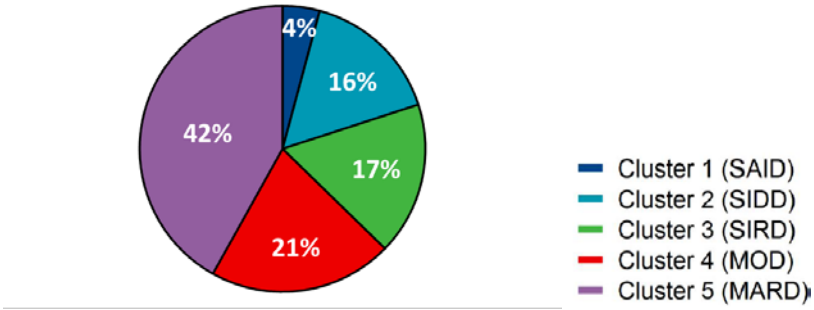
*Adjusted for age at trial entry

Application of clusters from the Swedish All New Diabetics in Scania cohort (ANDIS) to ADOPT

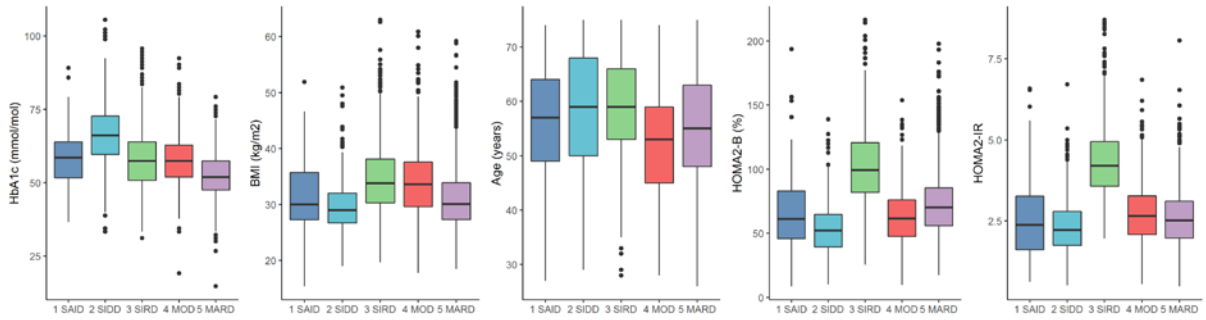
Supplementary Figure 10: Characteristics of clusters assigned in ADOPT from the cluster centre coordinates in ANDIS (n=4,003). Cluster centre coordinates originally published in Table S3, Ahlqvist et al., Lancet Diabetes Endocrinology 2018;6:361-69.

SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MOD=mild obesity-related diabetes. MARD=mild age-related diabetes. HOMA2-B=homoeostatic model assessment 2 estimates of β-cell function. HOMA2-IR=homoeostatic model assessment 2 estimates of insulin resistance.

(A) Distribution of ADOPT participants according to ANDIS clustering



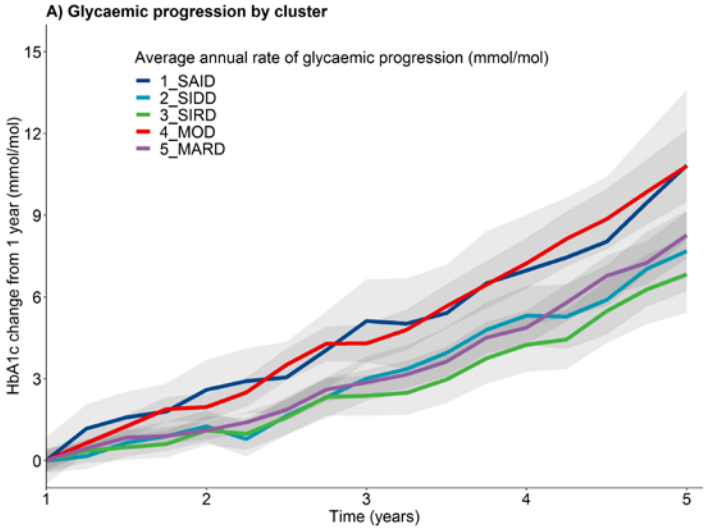
(B) Distributions of HbA1c, BMI, age at diagnosis, HOMA2-B, and HOMA2-IR at baseline for each ANDIS-derived cluster.



Supplementary Table 16: Concordance between clusters defined de-novo in ADOPT and clusters assigned in ADOPT from ANDIS cluster centre coordinates

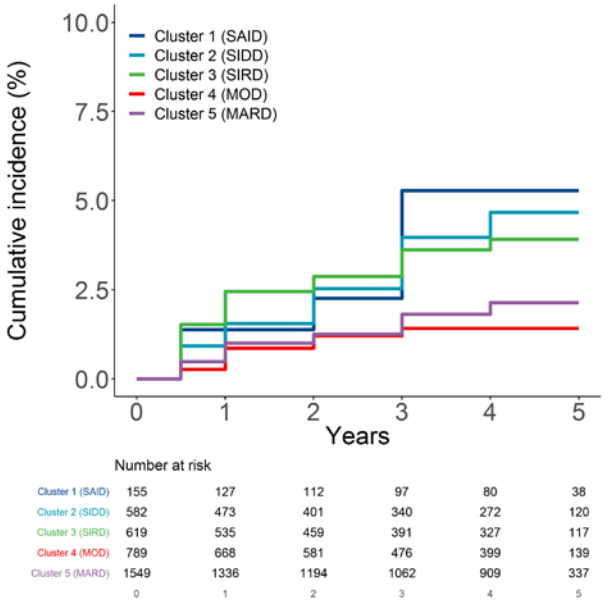
	ANDIS clusters				
ADOPT clusters	C1 (SAID)	C2 (SIDD)	C3 (SIRD)	C4 (MOD)	C5 (MARD)
C1 (SAID)	**100%**	0%	0%	0%	0%
C2 (SIDD)	0%	**56%**	9%	25%	9%
C3 (SIRD)	0%	1%	**59%**	2%	38%
C4 (MOD)	0%	2%	12%	**43%**	43%
C5 (MARD)	0%	11%	3%	18%	**68%**

Supplementary Figure 11: Glycaemic progression by cluster in ADOPT from one to five years using ANDIS-derived clusters (n=3,016)

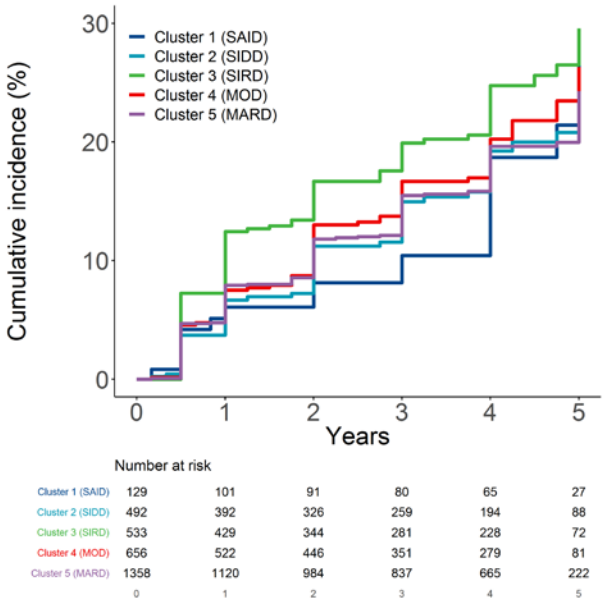


Supplementary Figure 12: Renal progression by cluster in ADOPT over five years using ANDIS-derived clusters.

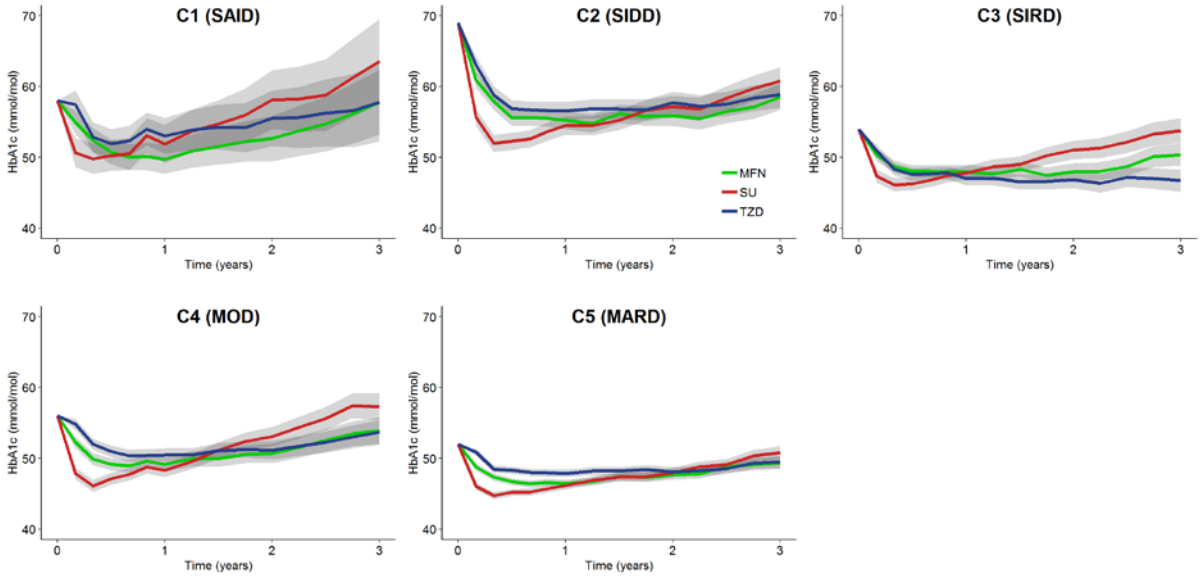
(A) Cumulative incidence of CKD Stage 3 (confirmed eGFR <60) in individuals with eGFR ≥60 at baseline (n=3,694). eGFR calculated using CKD-EPI formula.



(B) Cumulative incidence of albuminuria (UACR ≥30 mg/g) in individuals with UACR <30 mg/g at baseline (n=3,168).



Supplementary Figure 13: Change in HbA1c by drug for each cluster in ADOPT over three years using ANDIS-derived clusters (n=3,785). Adjusted mean HbA1c over three years by drug. Grey shading shows 95% CIs.



Supplementary Table 17: Model performance measures to compare clusters defined de-novo in ADOPT and clusters assigned in ADOPT from ANDIS cluster centre coordinates

A) Glycaemic progression from one to five years (n=3,016)

	R^2	AIC
ADOPT clusters	0.084	221404
ANDIS clusters	0.078	221446

B) Time to CKD Stage 3 (confirmed eGFR <60) in individuals with eGFR ≥60 at baseline (n=3,694). eGFR calculated using CKD-EPI formula.

	C-statistic	R^2
ADOPT clusters	0.58	0.01
ANDIS clusters	0.59	0.01

C) Time to albuminuria (UACR ≥30 mg/g) in individuals with UACR <30 mg/g at baseline (n=3,168).

	C-statistic	R^2
ADOPT clusters	0.52	0.002
ANDIS clusters	0.52	0.003

D) Explained variation (R^2) in treatment response (changes in HbA1c over 3 years)

	Metformin	Sulfonylurea	Thiazolidinedione
ADOPT clusters	0.15	0.20	0.17
ANDIS clusters	0.10	0.12	0.09

Chapter 7

Discussion

Chapter 7: Discussion

The work presented in this thesis evaluated the potential for a precision medicine approach in type 2 diabetes. We first described current and recent prescribing in the prescribing of glucose-lowering therapy in the UK for people with type 2 diabetes, and the relatively modest impact of recent prescribing changes on important short-term clinical outcomes including HbA_{1c} reduction and weight change after initiating new therapy.

We then explored the potential for a precision medicine approach with 4 common therapy options: DPP4 inhibitors, GLP1 receptor agonists, sulfonylureas and thiazolidinediones. Two studies demonstrated that routinely measured clinical characteristics are associated with glucose-lowering response to these therapies, with findings validated in independent datasets including randomised trials. Higher values of markers of insulin resistance are associated with lesser response to DPP4 inhibitors but are not associated with response to GLP1 receptor agonists. Female sex and higher BMI are associated with greater response to thiazolidinediones but lesser response to sulfonylureas.

We went on to evaluate whether the risks and benefits of therapy are associated. With sulfonylureas and thiazolidinediones, we found that increased glucose-lowering response is associated with an increased risk of common drug-specific side effects (respectively, hypoglycaemia and oedema). Finally, we compared a precision medicine strategy based on assigning individuals to type 2 diabetes subgroups with an individual-level strategy of using the specific clinical characteristics of individual patients to predict disease progression and treatment response, and found that the second ‘individual-level’ strategy had

greater clinical utility. This final study also provides an early insight into the potential population-level benefit of selecting treatment for individual people with type 2 diabetes based on their clinical characteristics.

This chapter gives an overview of the main findings of the thesis and discusses the works' conclusions, implications, limitations and potential areas for further research.

Chapter 2: Time trends in prescribing of type 2 diabetes drugs, glycemic control and risk factors: a retrospective analysis of primary care data, 2010-2017

The number of glucose-lowering medications available to patients and clinicians has increased markedly in recent years, and type 2 diabetes treatment guidelines have been updated to include a much greater choice of these medications. Despite this, up-to-date information on prescribing patterns and the impact of any changes in prescribing on the outcomes of people with type 2 diabetes is lacking.

In this study we described recent changes in prescribing of initial, second, third and fourth line medication for people with type 2 diabetes in the UK. We then estimated concomitant temporal changes in population-level short-term clinical outcomes: HbA_{1c} reduction, weight change, rates of hypoglycaemia, blood pressure change, and treatment discontinuation.

Conclusions

There have been drastic changes in the prescribing of glucose-lowering medication after first-line metformin. Most notably, use of DPP4 inhibitors second-line near doubled over 2010 to 2017 (41% of new prescriptions in 2017 compared to 22% 2010), while second-line use of sulfonylureas decreased (29% of new prescriptions in 2017 compared to 53% in 2010). SGLT2 inhibitor use increased rapidly following their introduction in 2013 for second to fourth line therapy; these agents comprised 17% of new first-fourth line prescriptions in 2017.

Despite the marked changes in prescribing we found relatively little change in short-term clinical outcomes over the same period. Average HbA_{1c} reduction

and the proportion of people discontinuing therapy were stable over the period studied, and although change in systolic blood pressure improved, this change was clinically small (for example, improvement in 6 month systolic blood pressure change 2017 vs. 2010 for second-line therapy: -2.1 mmHg (95% confidence interval -3.2;-2.0). Potentially clinical important improvements were observed in weight change second to fourth line, where use of SGLT2-inhibitors (which are associate with weight loss) increased, and in rates of recorded hypoglycaemia second-line, where use of sulfonylureas (known to cause hypoglycaemia) decreased.

Implication of Findings

This study provides timely ‘real-world’ information on recent prescribing trends for glucose-lowering medication in the UK, a setting where unlike many countries, such as the US, prescribing choice does not reflect the ability of people to pay for their medication. Interestingly, the marked changes in prescribing do not solely reflect changes in treatment guidelines, as they largely pre-empt the updates to UK NICE guidance that positioned DPP4 inhibitors (2015) and then SGLT2 inhibitors (2017) alongside sulfonylureas and pioglitazone as second and third-line treatment options.(1) This is in keeping with a recent study that found extensive geographical variation in prescribing of second-line therapy across the UK.(2) Taken together, these studies strongly suggest that the changes in prescribing are not entirely evidence based; possible external influences include local prescribing policy, drug safety awareness and pharmaceutical company marketing.(2)

To our knowledge, this is the first study to examine time trends in these clinical outcomes in the UK. The key finding is that, in terms of the clinical outcomes examined, the population-level impact of the change in prescribing towards

newer, more expensive medications has been relatively modest. For HbA_{1c} reduction the results are reassuring, given the increase second-line in use of DPP4-inhibitors which have been associated with lower glycaemic response compared to other agents in some studies.(3, 4) Similarly, improvements in weight change and a reduction in hypoglycaemia rates are likely to have led to improved quality of life for patients and a possible cost-benefit for the NHS.(5) However, these improvements should be considered in the context of the much higher cost of newer drug options. Based on the prescribing data we have presented and 2016 costs per drug in England the cost of treating diabetes second-line has doubled from on average £13 per prescription in 2010 to £27 per prescription in 2017.(6) Given the increasing prevalence of type 2 diabetes (estimated as over 3 million in England in 2015/16 compared to 2.3 million in 2010/11),(7) the trend towards prescribing of more expensive therapy has important implications for the NHS at a time budgets are constrained.

Subsequent work

The first and second line prescribing trends described in this study are similar to trends recently reported using the same dataset over a similar time period.(8) However, we are aware of no other studies that have examined third and fourth line prescribing, and no studies have used individual level data to examine concomitant changes in clinical outcomes alongside changes in prescribing.

The work in this chapter provides important context to subsequent chapters evaluating a precision medicine approach to guide type 2 diabetes therapy. The rapid changes in prescribing towards much more costly therapy after metformin highlights a consequence of a lack of clear guidance to inform treatment choice. Better understanding the risks and benefits of the treatment options commonly

prescribed after metformin offers the potential of more evidence based prescribing and improved clinical outcomes.

Limitations

A limitation of this study is the outcomes evaluated, given the recent evidence from placebo-controlled randomised trials of cardiovascular benefit with newer drug classes SGLT2 inhibitors and GLP1 receptor agonists an analysis of cardiovascular trends would be of considerable interest.(9) These trial results are directly applicable to 15-20% of individuals with type 2 diabetes and established cardiovascular disease.(4, 10)

A further limitation is the lack of available data to accurately capture hospital admission records of hypoglycaemia, or mild hypoglycaemia unrecorded in general practice. The absolute hypoglycaemia rates reported will therefore be an underestimate of the true population rates. However estimates of time trends are unlikely to be biased unless recording of hypoglycaemia has changed over time.

For HbA_{1c}, weight and blood pressure change there was substantial missing outcome data. This was mitigated by evaluation of 6 and 12 month outcomes (some individuals had a valid 6 month outcome but missing 12 month outcome and vice versa). Although, the characteristics of individuals included and excluded from the analysis were similar, we cannot be sure that differences between individuals with missing data did not account for our findings for the different outcomes assessed, thereby limiting the generalisability of the results of this study.

Future research

The findings complements other recent work which has suggested further studies are needed to evaluate the cost-effectiveness of increased prescribing of the newer glucose-lowering agents,(2) although this would require evaluation of cardiovascular outcomes as well at the outcomes reported here. Hospital episode linked (HES) linked data would facilitate this cardiovascular outcomes analysis and also allow examination of hospital admissions data for hypoglycaemia.

The fact that rapid changes in prescribing occurred without clear guidance highlights an important need for research that can establish a more evidence–based approach to selecting therapy. This could involve 1) comparative effectiveness analysis of the different drugs head-to-head using either prospective trials and/or observational data to better understand differences in average treatment effects 2) precision medicine evaluation of the relative benefits and risks of the different medications for individual patients.

Chapter 3: Precision Medicine in Type 2 Diabetes: Clinical Markers of Insulin Resistance Are Associated With Altered Short- and Long-Term Glycemic Response to DPP-4 Inhibitor Therapy

The previous chapter identified DPP4 inhibitors as the most commonly initiated second-line therapy at the end of 2017. This makes identification of clinical characteristics and biomarkers robustly associated with glucose-lowering response to DPP4 inhibitors a priority for any precision medicine strategy aiming to match therapy to people with type 2 diabetes likely to have the greatest drug response.

A major mechanism of action of DPP4-inhibitors is potentiation of pancreatic beta-cell insulin secretion. This aim of this chapter was to evaluate associations between markers of insulin secretion and resistance and glucose-lowering response to DPP4 inhibitor therapy.

Conclusions

The key finding of this chapter is that markers of higher insulin resistance were consistently associated with lesser glucose-lowering response after initiating DPP4 inhibitor therapy. This finding was demonstrated in the PRIBA prospective study (n=254), with validation in UK primary care data (CPRD, n=23,001). In PRIBA, baseline HbA_{1c} adjusted 6 month response was --5.3 mmol/mol (95%CI -1.8;-8.6) [-0.5% (95%CI -0.2;-0.8)] for a subgroup defined by obesity (BMI≥30) and high triglycerides (≥2.3mmol/L) [31% of participants], half that of a subgroup defined by non-obesity (BMI<30) and low triglycerides (<2.3mmol/L) [22% of participants; 6 month response -11.3 mmol/mol (95%CI -8.4;-14.1) [-1.1% (95%CI -0.8;-1.3)]].

Importantly, in PRIBA both non-routine (HOMA2 measured insulin resistance (HOMA2-IR)) and routinely available markers (BMI, triglycerides) showed consistency of effect. In CPRD, results for routinely available markers closely matched PRIBA. Associations were demonstrated to be independent of other clinical characteristics and were robust to sensitivity analysis including adjustment for co-therapy change (PRIBA only, in CPRD all individuals were on stable therapy) and stratification by sex. In contrast, there was no evidence of an association between markers of insulin resistance and glucose-lowering response for non-insulin treated individuals initiating GLP1 receptor agonists (PRIBA n=339, CPRD n=4,464).

Implication of Findings

The clinically relevant associations between markers of higher insulin resistance and reduced glycaemic response to DPP4 inhibitors suggests a potential role for using routine clinical characteristics to target DPP4 inhibitor therapy to those likely to have greater glycaemic response. BMI and triglycerides are available in clinical practice in the UK and many countries at no or little cost. This means use of these markers to identify people more or less likely to respond well to DPP4 inhibitors may be a cost-effective strategy even if the difference in likely glucose-lowering for many people is relatively modest. However, investigation of whether these and other clinical features are robustly associated with response to other glucose-lowering therapies is needed before the clinical utility of these findings can be fully evaluated.

Mechanistically, our results suggest there may be important differences between DPP4 inhibitors and the other incretin-based drug class, GLP1 receptor-agonists, for which there was no consistent association in non-insulin treated individuals for markers of insulin resistance.

Subsequent work

Although this study has informed several commentaries,(11-13) to our knowledge there have been no further published empirical studies testing the reported associations for DPP4-inhibitors in other datasets. We followed up this study in Chapter 4 to examine clinical factors associated with glucose-lowering response to sulfonylureas and thiazolidinediones, two other second-line options in current treatment guidelines.

Limitations

As many of the markers of insulin resistance collected in PRIBA are not routinely recorded, we were unable to validate several important associations in CPRD the validation dataset, notably fasting C-peptide and HOMA2-IR. Similarly, triglyceride measurements differed between the two studies; in PRIBA fasting measures were available, however in primary care most triglyceride measures are likely to be collected non-fasting. This may explain the diminished association between triglyceride levels and response in CPRD; alternatively the size of effect in PRIBA may be a chance finding.

We lacked follow-up beyond 6 months in PRIBA meaning we were unable to evaluate durability of response in the primary dataset. Durability (time to glycaemic failure, defined as >69 mmol/mol [8.5%]) was explored in CPRD using survival analysis, and although there were significant relative differences between obesity and triglyceride-defined subgroups differences were modest on the absolute risk scale. Any analysis of time to glycaemic failure in routine data is however especially limited by the likelihood of informative dropout (for example, if individuals with a poor 6 month response are more likely to then stop a therapy before a second HbA_{1c} is measured to confirm glycaemic failure). Missing data is a further limitation in CPRD, as 42% of individuals

initiating DPP4 inhibitor therapy then did not have a valid HbA_{1c} measure at 6 months so were not included in the analysis. We do not believe these individuals are likely to be missing at random, as the missing outcome data were likely to depend on their actual value (missing not at random). Replication of effect in independent datasets is therefore likely to provide a more robust strategy than multiple imputation.

Future research

GLP1 receptor agonists provided the only comparator group available in both datasets to demonstrate specificity of effect. An important area for future work is head to head evaluation with other second-line therapy options; sulfonylureas, SGLT2 inhibitors and thiazolidinediones. The ongoing TRIMASTER clinical trial will, using a crossover design, directly test the hypothesis that obese (BMI>30) participants will have a lesser response to the DPP4 inhibitor sitagliptin but a greater response to the thiazolidinedione pioglitazone compared to non-obese participants.(14)

Individual-level data from completed drug efficacy clinical trials are increasingly available to evaluate secondary research questions. This provides an important opportunity to further validate the associations identified in this study. Trials provide longer-term (up to 2 years) protocol-driven follow up with multiple regular HbA_{1c} measurements, facilitating use of more robust methods such as repeated measures mixed effects models to test associations and evaluate durability of effect. We are currently conducting analysis of several existing trials of DPP4 inhibitor therapy and results appear consistent with this analysis (Dennis, Shields, Jones, Hattersley; unpublished).

Although DPP4 inhibitors are thought to be a relatively safe treatment option and are not associated with weight gain,(15, 16) evaluation of differences between individuals in tolerance and risk of side-effects is a requirement for a clinically useful precision medicine approach. The small number of participants in PRIBA meant evaluation of these outcomes was not possible in this study, however existing protocol-driven trials and routine datasets are likely to provide the information required.

Chapter 4: Sex and BMI alter the benefits and risks of sulfonylureas and thiazolidinediones in type 2 diabetes: A framework for evaluating stratification using routine clinical and individual trial data

Sulfonylureas and thiazolidinediones are the two low-cost, off-patent, glucose-lowering therapies recommended after metformin in current treatment guidelines. In this chapter we used a novel research framework of 'discovery' in routine primary care data followed by validation in existing trial data to compare these two therapies head-to-head, and thus evaluate potential for applying a precision medicine approach based on likely glucose lowering response and risk of developing side-effects.

Conclusions

The key finding of this chapter is that sex and BMI are associated with marked differences in glucose lowering response to sulfonylureas and thiazolidinediones. More obese and female individuals respond better to thiazolidinediones, less obese and male individuals respond better to sulfonylureas. Differences were first observed for 12 month response in primary care data (CPRD, n=22,379), and then confirmed up to 5 years for four subgroups defined by sex and obesity (BMI </≥30) in two large trials in which participants were randomised to therapy (ADOPT and RECORD, n=4,947). Importantly, these subgroups also differed in weight change and risk of side-effects. In particular, with thiazolidinediones obese females had a much greater response relative to sulfonylureas but were also at increased risk of oedema and had much greater weight gain.

Implication of Findings

To our knowledge this is the first robust demonstration of differential response when directly comparing two type 2 diabetes therapy options, and the first study to evaluate systematically how the benefits and risk of type 2 diabetes therapy vary with clinical characteristics. The results suggest that, if the clinical decision is between sulfonylureas and thiazolidinediones, it is possible to robustly identify people that are likely to have a much greater glucose-lowering response with one agent over the other.

This study also demonstrates that precision medicine cannot just be focused on the likely benefits of therapy. With thiazolidinediones, risk of side-effects and weight change appeared to increase with greater glucose-lowering response. Even using relatively crude subgroups we were able to provide information on likely risks and benefits that are more tailored to individuals than the current approach based on average outcomes.

This study also presents a novel, practical, and low-cost methodological framework for evaluating a precision medicine approach in type 2 diabetes without the need for expensive prospective studies. Drug efficacy trial data for the major drug options after metformin are now available upon application from open research portals.(17, 18) The framework using routine data and trial data is potentially applicable in many other chronic diseases where precision medicine is of interest and there are multiple treatment options, for example hypertension and epilepsy.

Subsequent work

Chapter 5 extends the evaluation of risks and benefits for the two therapies by specifically examining associations between glucose-lowering response and

risk of side-effects; the analysis in the current chapter suggested an association based on subgroup estimates but did not formally test this. In Chapter 6 we also examine the clinical utility of selecting glucose-lowering treatment based on subgroups with an approach using a model that combines continuous patient clinical features.

Limitations

Methodologically, a limitation of this analysis is the subgroup based approach used, in particular the dichotomisation of BMI into obese and non-obese categories. The main advantage of a subgroup based approach is in terms of presentation and interpretation of results, which in this study was an important factor as it is an early demonstration of the potential of precision medicine in type 2 diabetes. Statistically, there are however significant drawbacks to applying cut-offs to define subgroups compared with using continuous measures, most notably a substantial loss of statistical power.(19, 20)

Whilst in this study clear and consistent differences for glycaemic response between subgroups were observed, a clear disadvantage to this modelling approach is the assumption that individuals within a subgroup are homogenous. For example, a male with a BMI of 30.1 was estimated to have the same response as a male with BMI of 40.1. This may or may not be the case but it cannot be tested using the subgroups defined in this study. This limits the clinical utility of the reported subgroups, although it does not diminish the main finding: that glucose-lowering response varies predictably by easily measured clinical characteristics.

Use of subgroups also further reduced power to evaluate differences between people in risk of side-effects. For this reason further formal evaluation of the

association between response and risk of side-effects was conducted in Chapter 5.

Further limitations of this study include the limited range of characteristics evaluated. The study focused on sex and BMI as these were the routine clinical factors associated with the greatest differential response in primary care data; however duration of diabetes and, to a lesser extent, HDL were also associated with differential response (Chapter 4, Supplementary Figure S3). Older age at diagnosis was associated with greater response to both drugs, suggesting a utility for prediction of response but not for guiding decisions on therapy. As well as sex and BMI, evaluation of a broad range of clinical characteristics across all relevant therapy options will be required for a comprehensive evaluation of the potential of a precision medicine approach to type 2 diabetes therapy.

Future research

This study and the previous study reported in Chapter 3 have demonstrated BMI is a potential key clinical measure for guiding therapy. Higher BMI has been found to be associated with lesser response to both DPP4 inhibitors and sulfonylureas. Head-to-head evaluation of these two drug classes would be of great interest to determine if the size of effect is comparable or if at higher BMI levels one drug class is superior to the other.

A key strength of this study is replication of effect across 3 independent datasets. However, to ultimately confirm the results a blinded prospective trial with one arm allocated therapy based on their sex and obesity and the other arm randomised without allocation would be required. Given the methodological limitations of using subgroups and the limited therapies evaluated this is not likely to be a cost-effective or practical study. Instead, more appropriate use of

the results would be to inform the development of a model incorporating multiple validated continuous clinical features to predict response to multiple therapies. The model could then be used to select the optimal medication(s) for individuals based on likely glucose-lowering. The model could then be tested prospectively to examine to what degree selection of medication based on likely glucose-lowering alters glycaemic response as well as secondary outcomes such as weight change and development of side-effects.

Finally, for thiazolidinediones, although CPRD data suggested a class effect, it would be of interest to validate findings in trials of pioglitazone. Both ADOPT and RECORD used rosiglitazone which has the same principal mechanism of action as pioglitazone but is no longer used in clinical practice in many countries. Pioglitazone trial data was requested for this study but was not made available by Takeda.

Chapter 5: Evaluating associations between the benefits and risks of drug therapy in type 2 diabetes: A joint modelling approach

The previous chapter suggested people with increased glycaemic response may be at increased risk of developing side effects with thiazolidinedione therapy in particular, but did not test this directly. No methodological framework has previously been proposed for direct evaluation of the association between the benefits and risks of drug therapy. In this chapter we applied joint longitudinal-survival modelling to formally evaluate the association between glycaemic response over time (a longitudinal process) and the risk of common side effects (a time-to-event process) for metformin, thiazolidinedione and sulfonylurea therapy in the ADOPT blinded randomised trial (n=4,351).

Conclusions

For sulfonylurea and thiazolidinedione therapy, estimates from joint models suggested greater glycaemic response was associated with an increased risk of developing side-effects (respectively, hypoglycaemia and oedema). In contrast, with metformin there was no evidence that greater response was associated with an increased risk of gastrointestinal side-effects.

Implication of Findings

Joint modelling was a useful approach to directly evaluate associations between the benefits and risks of type 2 diabetes drug therapy. The findings for sulfonylurea and thiazolidinedione therapy suggest application of a precision medicine strategy to target therapy at people likely to respond well without being at increased risk of developing side-effects will be difficult. This may only be possible if future studies can identify biomarkers or clinical features association with either, but not both, greater response and lower risk of side-

effects. Joint models provide an ideal framework to identify such markers. However, an important point is that the results of this study do not preclude a precision medicine approach for sulfonylureas and thiazolidinediones, as decision making should be based on absolute rather than relative estimates of risk or benefit.(21, 22) It may be that individuals can still be identified who are likely to respond well to these drugs without being at substantially increased absolute risk of side-effects.

Joint modelling is an analytic approach generalisable to any set of longitudinal efficacy markers and associated set of adverse events. This study suggests an opportunity for a much more general application of joint modelling to more robustly evaluate the benefits and risk of therapy of medications in double blinded trials, like ADOPT, where participants are randomised to therapy. This would apply to most drug efficacy trials, in diabetes and in other diseases. Currently in drug efficacy trials side-effects are typically reported as a simple table contrasted with the placebo arm, with no temporal information, and potential associations between side-effects and drug response are not evaluated. A key advantage of joint models for this purpose is their flexibility. As demonstrated in this study different parameterisations of joint models offered differed insights into the underlying nature of response:side-effect associations. Correctly parameterised joint models are likely to be more efficient and less biased than standard approaches as they capture the true, unobserved, biomarker trajectory.(23) This suggests they may be an especially valuable method in smaller datasets such as clinical trials.

Subsequent work

We are aware of no studies published that have used joint modelling or alternative approaches to test associations between the benefits and risks of drug therapy in type 2 diabetes.

Limitations

Limitations of this analysis include the absence of a replication dataset. Data from primary care were not included due to concerns over the influence of recording bias, as discussed below. As this is the first application of joint-modelling in this context we did not consider more complicated joint models, for example we did not consider time-varying associations which may be relevant for progressive side-effects that develop over time. We did also not incorporate changes in drug dose, which may have provided further insight into response:side-effect associations. Full elaboration of these and other challenges in a more general mathematical presentation of joint modelling of risks and benefits of drug therapy would be of considerable interest.

Future research

Evaluation of associations between risks and benefits of therapy for the newer glucose-lowering medications would be of considerable interest. A further key question is whether joint modelling provides a useful framework to evaluate the association between drug response and risk of side-effects in ‘real-world’ primary care datasets where a much wider range of people are initiated on glucose-lowering medications compared to the trials which have restricted inclusion criteria. However, in primary care follow-up is not protocol driven, meaning HbA_{1c} and side-effects are recorded less frequently and systematically than in trials. There may also be recording biases, for example if more

conscientious individuals are more likely to 1) take their medication and so attain better glycaemic response; 2) attend their general practice and have their HbA_{1c} recorded; 3) report side-effects during their general practice visit.

We have conducted initial evaluation of the joint modelling approach in primary care data (CPRD). Achieving model convergence has been a major challenge due to the much larger sample size. With the potential challenges discussed above in mind, we have implemented negative control analysis by testing associations between response and risk of a side-effect for individuals initiating drugs not expected to cause that particular specific side-effect. This has revealed a common finding that side-effects and response are often positively associated, regardless of drug (Dennis, Henley, unpublished). These early results suggest recording bias may limit inferences into the association between benefits and risks of drug therapy in routine primary care data. It may be that this question can only be evaluated in blinded trial datasets where recording biases should be minimal.

Chapter 6: Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared to models based on simple clinical features: an evaluation using clinical trial data

A recent study proposed a novel substratification of diabetes, using a data-driven cluster analysis in Scandinavian registry data to identify five reproducible subgroups of adult-onset diabetes.(24) The authors went on to show differences between the clusters in disease progression and risk of complications in observational follow-up. The authors suggested the clusters might help with therapy selection in the future but did not test whether the clusters could inform therapy choice.

This chapter aimed to test the clinical utility of the proposed data-driven cluster approach.(24) The cluster analysis was repeated, and differences by cluster in disease progression and treatment response were evaluated in participants in the ADOPT and RECORD trials with randomised, protocol-driven follow-up data available. We then compared the utility of simpler clinical measures to the clusters for stratifying each outcome assessed.

Conclusions

The proposed clusters were reproducible in trial data and did differ in progression and treatment response. However, the key finding of this chapter is that simpler routine clinical measures were as or more useful than the clusters for stratifying each outcome assessed. In particular, models developed in ADOPT using just 4 simple clinical features (sex and continuous measures of BMI, age at diagnosis and baseline HbA_{1c}) markedly outperformed the clusters to select therapy for individuals in the independent dataset RECORD.

Implication of Findings

People with type 2 diabetes differ in treatment response and risk of disease progression, raising the possibility of a practical, clinically orientated stratified approach in the near future. Our study suggests a ‘prediction model’ approach, combining phenotypic measures to predict specific outcomes for individual patients, is likely to have greater clinical utility than approaches that use clinical features to assign individuals into subgroups. Even four simple measures combined in a multivariable model showed the potential to improve glycaemic response if used to select therapy for individual patients.

Subsequent work

Prior to submission we searched Scopus, Web of Science, and Google Scholar to track the citations of the original Scandinavian study that proposed the subgroups, searching for follow-up studies assessing the reproducibility, clinical utility and role in treatment selection of the proposed data-driven clusters up to January 1, 2019. We identified a study that identified similar clusters in Chinese and a small mixed American population but did not examine any aspect of clinical utility as clinical follow-up was not available.(25) A second study of Danish people applied similar cluster analysis and, with duration of diabetes as an additional input variable, identified five subgroups of type 2 diabetes that differed to those in the original study, and differed in the prevalence of diabetes complications.(26) No studies were found that tested the clinical utility and particularly the role in treatment of the proposed cluster-based approach.

Limitations

A limitation of this study is the original exclusion criteria of the trials, with exclusions at screening based on clinical variables that informed the cluster analysis (blood glucose levels and age (and BMI in RECORD)). Despite this the clusters were identifiable with a very similar pattern of differences in clinical characteristics to the original study and with a similar proportion of individuals allocated to each cluster. The trial design, sample size and limited follow-up meant power was limited to evaluate heterogeneity in cardiovascular outcomes or other complications such as retinopathy.

Future research

This analysis suggests a number of follow up studies relating to precision medicine in type 2 diabetes. Age alone was identified as a useful predictor of glycaemic progression, in keeping with a recent observational study,(27) and further evaluation of predictors of progression in trial datasets with protocol driven long-term follow-up would be of considerable interest.

It would also be interesting to see how the recently proposed genetically defined type 2 diabetes clusters of Udler and colleagues performed in a similar study,(28) although genetic information was not collected in RECORD or ADOPT and so other trial datasets will be required.

The approach to evaluate treatment selection used in this study has not been widely applied elsewhere but is based on recent methodological developments.(29) Standard performance measures are focused on the ability of a model to predict response and this is of limited utility for treatment selection, as factors that predict response are much less useful than factors that predict differential response between therapies. It would be interesting to

explore the robustness of the treatment selection strategy proposed in future work. On promising method is the ‘concordance-statistic for benefit’ metric put forward by van Klaveren and colleagues; this method aims to measure the performance of a model to predict treatment benefit when comparing two therapies or a therapy with placebo.(30)

Final remarks

This thesis demonstrates that routinely measured clinical features offer great potential to inform a precision medicine approach to aid the selection of glucose-lowering therapy for people with type 2 diabetes. For DPP4 inhibitors, sulfonylureas and thiazolidinediones, the studies in this thesis have identified simple features that robustly predict differential glucose lowering response to a potentially clinically significant degree. Initial work has also been undertaken to evaluate differences between people in the risk of side-effects. Future research is required to evaluate the other second-line option in the UK, SGLT2 inhibitors, as well as to further evaluate GLP1 receptor agonists which are now positioned as early treatment options in US/European guidelines.(4)

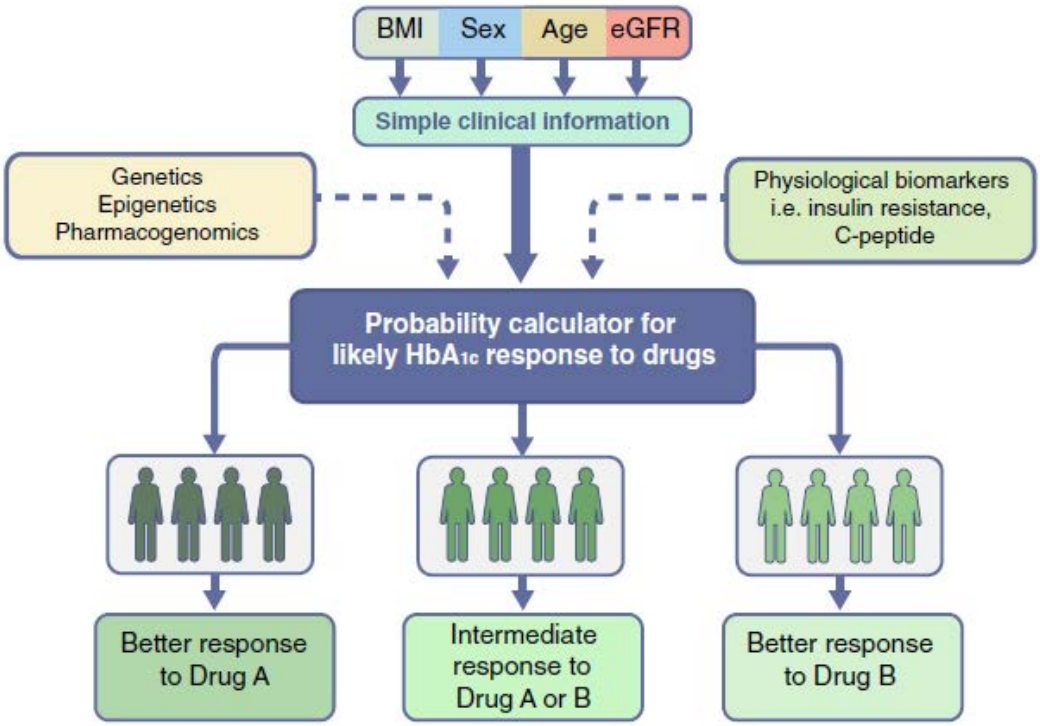
Methodologically, the work in this thesis has demonstrated that trial and routine care datasets provide much of the data required to evaluate clinical factors associated with differential treatment effects of the different glucose-lowering therapies. A framework of discovery in routine data with validation in existing trial datasets offers a low-cost and principled way to evaluate the potential of precision medicine in this area, without the need for expensive and time consuming prospective trials. Starting with primary care data ensures that, in the first instance, the focus is on the utility of routine clinical features available at no or little cost to any doctor. Non-routine biomarkers and ‘omic’ approaches can then be integrated to this basic model if clinically relevant effects can be robustly demonstrated.

This work also highlights the critical importance of evaluation of not just the benefits but also the risks of therapy. We have demonstrated that joint modelling offers a useful framework to test whether glucose-lowering response and side-effects are associated. However ultimately for individuals it is the

absolute risk of side-effects compared to the likely glucose-lowering response that can provide the most useful information to guide decision making.

The comparison of cluster analysis defined subgroups with models that combine multiple continuous features suggests that there is likely to be greater clinical utility from continuous feature models than type 2 diabetes subgroups. Continuous feature models will require integration of multiple differential features in a multivariable model, to enable separation of likely response between the different glucose-lowering therapies (Figure 1).

Figure 1: Treatment response based precision medicine approach based on combining multiple continous clinical features. Reproduced under open licence from Hattersley and Patel, Diabetologia 2017.(31)



Whether the effect sizes using a multivariable model to predict either glucose-lowering response or side-effects are large enough to guide therapy is an

important area for future research. Effect sizes are likely to be relatively modest for many individuals, in contrast to those observed in monogenic diabetes where specific genetic mutations result in up to 5-fold differences in treatment response.(32) For individuals for whom effect sizes are modest, this information is still important as it can provide an evidence-base for selecting therapy based on other key criteria, in particular cost and patient preference. Future research is also required on the acceptability of provision of this personalised information to clinicians and patients, and the most effective ways to communicate this. Ultimately, a prospective trial to test the utility of a treatment selection model as a decision aid for clinicians will be required.

Given the recent demonstration of cardiovascular benefit for SGLT2 inhibitors and GLP1 receptor agonists, evaluation of differences between people in cardiovascular outcomes is now of clear importance alongside glucose-lowering and side-effects. Ultimately, integration of these three elements, alongside cost and patient preference, may in the near future allow a truly ‘precise’ approach to selecting therapy for people with type 2 diabetes.

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